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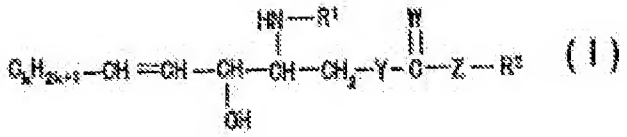
Abstract of **WO 0138295 (A1)**

Translate this text

Sphingosine derivatives represented by general formula (I), or pharmaceutically acceptable salts thereof, wherein R<1> and R<2> are each hydrogen or the like; Z is NR<7> (wherein R<7> is hydrogen or the like); Y is oxygen or NR<8> (wherein R<8> is hydrogen or the like); W is oxygen or sulfur; and k is an integer of 1 to 20. The derivatives and the salts are useful as preventive or therapeutic drugs for cerebrovascular disorders such as cerebral hemorrhage and cerebral infarction; head injuries; senile dementia; degenerative diseases of cranial nerve such as Alzheimer disease and Parkinson disease; diabetes; obesity; arteriosclerosis; inflammatory diseases; immunologic diseases; cancers; kidney diseases; and heart diseases.



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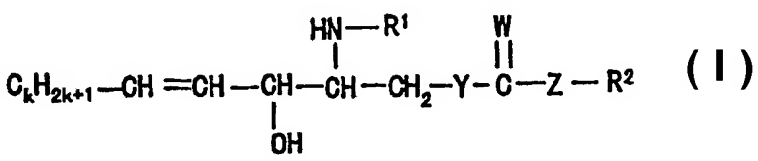
(54) Title: SPHINGOSINE DERIVATIVES

(54) 発明の名称: スフィンゴシン誘導体



(I)

(57) Abstract: Sphingosine derivatives represented by general formula (I), or pharmaceutically acceptable salts thereof, wherein R^1 and R^2 are each hydrogen or the like; Z is NR^7 (R^7 is hydrogen or the like); Y is oxygen or NR^8 (R^8 is hydrogen or the like); W is oxygen or sulfur; and k is an integer of 1 to 20. The derivatives and the salts are useful as preventive or therapeutic drugs for cerebrovascular disorders such as cerebral hemorrhage and cerebral infarction; head injuries; senile dementia; degenerative diseases of cranial nerve such as Alzheimer disease and Parkinson disease; diabetes; obesity; arteriosclerosis; inflammatory diseases; immunologic diseases; cancers; kidney diseases; and heart diseases.

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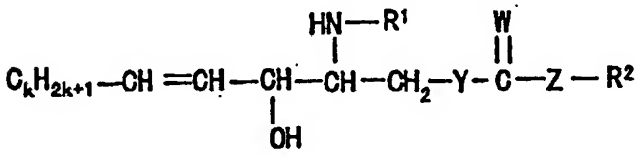
(57) 要約:

式



[式中、R^1、R^2は水素原子等であり、ZはNR^7（R^7は水素原子等である。）であり、Yは酸素原子又はNR^8（R^8は水素原子等である。）であり、Wは酸素原子又は硫黄原子であり、kは１～２０の整数である。]で表されるスフィンゴシン誘導体又はその薬学的に許容される塩。

本発明の化合物は脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防薬、治療薬として使用できる。

明細書

スフィンゴシン誘導体

技術分野

本発明は、中性スフィンゴミエリナーゼを阻害することにより各種医薬として有用な新規スフィンゴシン誘導体に関する。

背景技術

スフィンゴミエリナーゼは主に細胞膜に存在するスフィンゴ脂質の一つであるスフィンゴミエリンを基質として、セラミドとホスホコリンに分解する酵素であり、その活性発現の至適ｐＨから酸性タイプと中性タイプとに大別される。酸性タイプがリソゾームに局在するのに対し、中性タイプは細胞膜あるいは細胞質に存在するが、両タイプ共にスフィンゴミエリンの代謝によるセラミドの生成に関与していると考えられている。

スフィンゴミエリナーゼにより生成されるセラミドは脂質セカンドメッセンジャーとしてアポトーシス、細胞増殖、分化等の種々の細胞機能において重要な役割を果たしており、この代謝産生経路はスフィンゴミエリン経路と呼ばれている。

スフィンゴミエリナーゼは虚血、ＴＮＦ－α、ＩＬ－１β、ＩＦＮ－γ、１α，２５－ジヒドロキシビタミンD_3、抗癌剤あるいは放射線等の各種ストレスにより活性化されることから、これらの化学的・物理的ストレスがその発症・進展の原因である各種病態にスフィンゴミエリン経路が関与していることが考えられる。例えば、脳虚血時にはスフィンゴミエリン経路が活性化されるが、脳神経細胞へのスフィンゴミエリナーゼあるいはセラミドの添加はアポトーシスによる細胞死を引き起こす。また、脳虚血時にはＴＮＦ－αやＩＬ－１βの産生が亢進し、神経細胞死が誘発されるが、ＴＮＦ－αの可溶化受容体やＩＬ－１βの受容体拮抗剤は虚血による神経細胞死を抑制する。

上記脳血管障害以外にも頭部外傷、老人性痴呆、アルツハイマー病、パーキンソン氏病等の脳神経変性疾患に広くＴＮＦ－αやＩＬ－１βの産生亢進が関与している。

非インスリン依存性糖尿病及び肥満では脂肪細胞でのＴＮＦ－αの産生が亢進し、インスリン抵抗性が誘導されるが、これにはＴＮＦ－αによるスフィンゴミエリン経路の活性化が関与している。また、ＩＬ－１βはインスリン依存性糖尿病の発症に関与するが、セラミドはＩＬ－１βと同様の作用を発現する。

ＴＮＦ－α及びＩＬ－１βは動脈硬化の発症・進展の過程にも関与する。すなわち、ＴＮＦ－α及びＩＬ－１βは血管内皮細胞において接着因子のＩＣＡＭ－１を発現させ、単球の血管内皮細胞への接着や内皮下への遊走を促進する。更に、ＴＮＦ－αはスフィンゴミエリン経路の活性化を介して血管内皮細胞のアポトーシスを引き起こす。また、スフィンゴミエリン経路の活性化は血管平滑筋でのＬＤＬ凝集を促進し病変を形成すると共に、血管平滑筋のアポトーシスを介してプラークを不安定化させる。

炎症免疫系細胞でのセラミドの生理活性は非常に多彩であり、Ｔ細胞及びＢ細胞の分化・活性化、各種サイトカイン産生、アポトーシスの誘導、炎症性プロスタグランジンの産生等を介して各種炎症性疾患及び免疫性疾患の発症・進展に深く関与している。また、スフィンゴミエリン経路の活性化にはＴＮＦ－αやＩＬ－１βをはじめ非常に多くの化学的・物理的ストレスが関与することから、これらの病態には多くの細胞系及びシグナル経路が互いに複雑にクロストークしているものと考えられる。

以上のことから、スフィンゴミエリナーゼに対する特異的な阻害剤は、脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防薬、治療薬として使用できる。

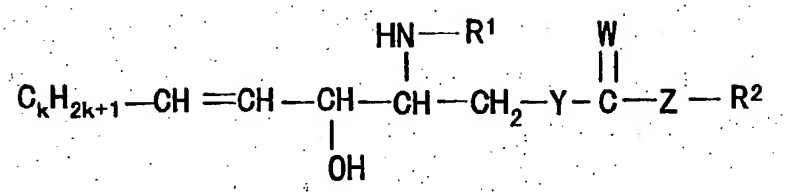
スフィンゴミエリナーゼ阻害作用を有するスフィンゴシン誘導体として３-Ｏ-アルキルスフィンゴミエリンが報告されているが（Mark D.Lister,et al.,Biochimica et Biophysica Acta,1995,1256,25）、本発明の化合物と化学構造が異なる。

発明の開示

本発明は、スフィンゴミエリナーゼ阻害作用を有する新規な化合物を提供する

ことを目的として、鋭意研究を進めた結果、ある種のスフィンゴシン誘導体が中性スフィンゴミエリナーゼ阻害活性を有することを見出し、本発明を完成した。

すなわち、本発明は一般式（Ｉ）



[式中、R^1は水素原子、C_{2-20}アルカノイル基、ベンゾイル基、「ハロゲン原子、C_{1-5}アルキル基、水酸基、C_{1-5}アルコキシ基、C_{2-5}アルカノイル基、カルボキシル基、C_{2-5}アルコキシカルボニル基、アミノ基、C_{1-5}アルキル基の１若しくは２個で置換されたアミノ基、C_{2-5}アルカノイルアミノ基、C_{2-5}アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたC_{1-5}アルキル基、シアノ基、ニトロ基、メルカプト基又はC_{1-5}アルキルチオ基」で置換されたベンゾイル基、C_{4-8}シクロアルキルカルボニル基、C_{2-20}アルコキシカルボニル基、式－ＣＯＣ$(R^3)_2$ＮＨR^4（式中、R^3は水素原子又はC_{1-5}アルキル基であり、R^4は水素原子又はC_{2-5}アルコキシカルボニル基である。）で示される基又は式－ＣＯＣO_2R^3（式中、R^3は水素原子又はC_{1-5}アルキル基である。）で示される基であり、R^2は水素原子、C_{1-8}アルキル基、式－$(CH_2)_nR^5$（式中、R^5は水酸基、アミノ基、C_{1-5}アルキル基の１～３個で置換されたアミノ基、カルボキシル基、C_{2-5}アルコキシカルボニル基、カルバモイル基、C_{1-5}アルキル基の１若しくは２個で置換されたアミノカルボニル基、カルバモイルオキシ基、C_{1-5}アルキル基の１若しくは２個で置換されたアミノカルボニルオキシ基、フェニル基、「ハロゲン原子、C_{1-5}アルキル基、水酸基、C_{1-5}アルコキシ基、C_{2-5}アルカノイル基、カルボキシル基、C_{2-5}アルコキシカルボニル基、アミノ基、C_{1-5}アルキル基の１若しくは２個で置換されたアミノ基、C_{2-5}アルカノイルアミノ基、C_{2-5}アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたC_{1-5}アルキル基、シアノ基、ニトロ基、ウレイド基、C_{1-5}アルキル基の１若しくは２個で置換されたウレイド基、メルカプト基又はC_{1-5}アルキルチオ

基」で置換されたフェニル基、ピリジル基、C_{1-5}アルコキシ基で置換されたピリジル基、ピラジル基、ピロリジル基、ピペリジル基、ピペラジル基、モルホリニル基、チオモルホリニル基、イミダゾリル基、チアゾリル基、チアジアゾリル基、テトラゾリル基、キノリル基又は１Ｈ－インダゾリル基であり、ｎは０～５の整数である。）で示される基又は式－SO_mR^6（式中、R^6はフェニル基又は「ハロゲン原子、C_{1-5}アルキル基、水酸基、C_{1-5}アルコキシ基、C_{2-5}アルカノイル基、カルボキシル基、C_{2-5}アルコキシカルボニル基、アミノ基、C_{1-5}アルキル基の１若しくは２個で置換されたアミノ基、C_{2-5}アルカノイルアミノ基、C_{2-5}アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたC_{1-5}アルキル基、シアノ基、ニトロ基、ウレイド基、C_{1-5}アルキル基の１若しくは２個で置換されたウレイド基、メルカプト基又はC_{1-5}アルキルチオ基」で置換されたフェニル基であり、ｍは０、１又は２である。）で示される基であり、ＺはＮR^7（ここで、R^7は水素原子、水酸基又はC_{1-5}アルキル基である。）であり、Ｙは酸素原子又はＮR^8（R^8は水素原子、水酸基又はC_{1-5}アルキル基である。）であり、Ｗは酸素原子又は硫黄原子であり、ｋは１～２０の整数である。]で表わされるスフィンゴシン誘導体又はその薬学的に許容される塩である。

本発明において、C_{2-20}アルカノイル基とは炭素原子数２～２０の直鎖又は分岐鎖状のアルカノイル基を意味し、例えばアセチル基、プロパノイル基、イソプロパノイル基、ブチリル基、イソブチリル基、バレリル基、ピバロイル基、ミリスチリル基、ステアリル基などを挙げることができる。

C_{2-5}アルカノイル基とは前記のうち炭素原子数が２～５のものを意味する。

C_{4-8}シクロアルキルカルボニル基とは炭素原子数４～８のシクロアルキルカルボニル基を意味し、例えばシクロプロピルカルボニル基、シクロペンチルカルボニル基、シクロヘキシルカルボニル基、シクロヘプチルカルボニル基などを挙げることができる。

C_{2-5}アルコキシカルボニル基とは炭素原子数２～５の直鎖又は分岐鎖状のアルコキシカルボニル基を意味し、例えばメトキシカルボニル基、エトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、tert－ブトキシカル

ボニル基などを挙げることができる。

C_{1-20}アルキル基とは炭素原子数１～２０の直鎖又は分岐鎖状のアルキル基を意味し、例えばメチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、tert－ブチル基、ペンチル基、イソペンチル基、ヘキシル基、イソヘキシル基、ヘプチル基、オクチル基、ノニル基、デシル基、トリデシル基、ノナデシル基などを挙げることができる。

C_{1-8}アルキル基とは前記のうち炭素原子数１～８のものを意味し、C_{1-5}アルキル基とは前記のうち炭素原子数１～５のものを意味する。

C_{1-5}アルキル基の１～３個で置換されたアミノ基とはアミノ基の窒素原子がC_{1-5}アルキル基で置換されていることを意味し、３個置換されているとは４級塩であることを意味する。

C_{2-5}アルカノイルアミノ基とはアミノ基の窒素原子がC_{2-5}アルカノイル基の１個で置換されていることを意味し、例えばアセチルアミノ基、イソプロピオニルアミノ基などを挙げることができる。

C_{2-5}アルコキシカルボニルアミノ基とはアミノ基の窒素原子がC_{2-5}アルコキシカルボニル基の１個で置換されていることを意味し、例えばメトキシカルボニルアミノ基、ブトキシカルボニルアミノ基などを挙げることができる。

ハロゲン原子とは、フッ素原子、塩素原子、臭素原子又はヨウ素原子である。

ハロゲン原子の１～５個で置換されたC_{1-5}アルキル基とは前記ハロゲン原子で置換された炭素原子数１～５の直鎖又は分岐鎖状のアルキル基を意味し、例えばトリフルオロメチル基などを挙げることができる。

C_{1-5}アルコキシ基とは炭素原子数１～５の直鎖又は分岐鎖状のアルコキシ基を意味し、例えばメトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、ヘプトキシ基などを挙げることができる。

C_{1-5}アルキルチオ基とは炭素原子数１～５の直鎖又は分岐鎖状のアルキルチオ基を意味し、例えばメチルチオ基、エチルチオ基、プロピルチオ基、イソプロピルチオ基、ブチルチオ基、イソブチルチオ基、tert－ブチルチオ基、ペンチルチオ基、ヘキシルチオ基などを挙げることができる。

水酸基の保護基としては、アセチル基、ベンゾイル基等のアシル基；トリメチルシリル基、t-ブチルジメチルシリル基、ベンジルジメチルシリル基等の三置換シリル基；テトラヒドロピラニルオキシ基、メトキシメチル基等のアセタール型保護基などを挙げることができる。

なお、一つの一般式中に複数の同一記号で表される置換基が存在する場合には、それらは同一であっても異なっていても良い。

薬学的に許容される塩類とは、酸あるいはアルカリ付加塩を示す。この場合使用する酸又はアルカリに特に制限はないが、酸としては塩酸、硫酸、硝酸、酢酸、ベンゼンスルホン酸などを挙げることができ、アルカリとしてはナトリウム、カリウム等の金属イオン、アルキルアンモニウムなどのアンモニウムイオンなどを挙げることができる。

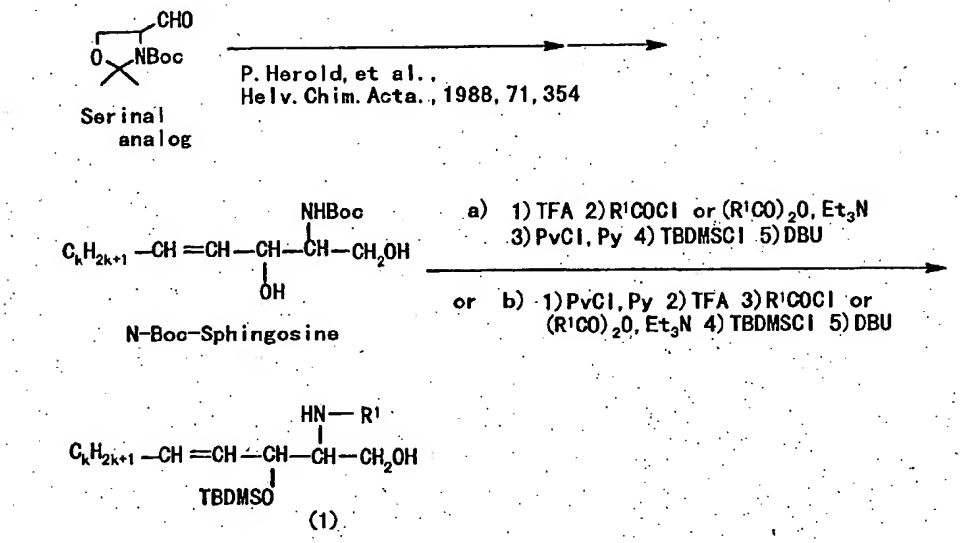
本発明の化合物は単一の光学活性体であっても、あるいは立体異性体の混合物であってもよい。

本発明の化合物は、例えば下記に示す方法に従って製造することができる。

以下、本明細書中では、Bocはtert-ブトキシカルボニル基、TFAはトリフルオロ酢酸、Pvはピバロイル基、DBUは１,８-ジアザビシクロ[５.４.０]ウンデセ-７-エン、TCFはクロロぎ酸トリクロロメチル、TBDMSはtert-ブチルジメチルシリル基、WSC･HClは１-エチル-３-(３-ジメチルアミノプロピル)カルボジイミド塩酸塩、HOBtは１-ヒドロキシベンゾトリアゾールを、それぞれ表わすことがある。

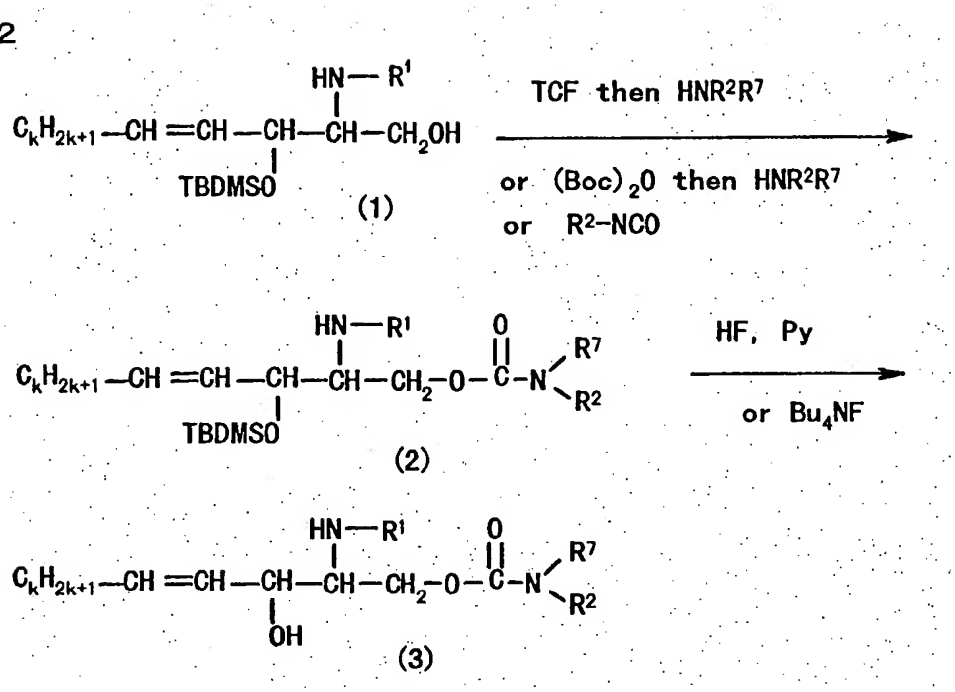
まず、合成原料であるN-Boc-スフィンゴシンは、P.Heroldらの方法（Helv.Chim.Acta.,1988,71,354）に従いセリナールより合成し、次いで式１に示した方法により、中間化合物(1)を合成することができる。

式1



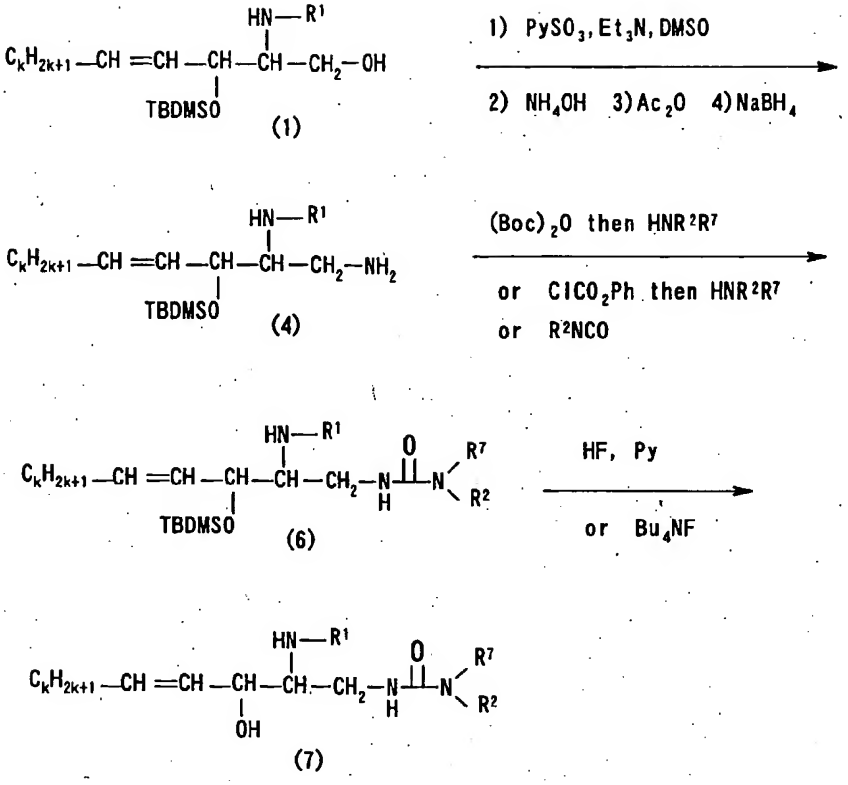
一般式（Ｉ）の化合物において、Ｙ及びＷが酸素原子でありＺがＮＲ^{7}である化合物(3)は、式２に示した方法により製造することができる。すなわち、化合物(1)を、塩基存在下クロロぎ酸トリクロロメチルあるいは二炭酸ジ-tert-ブチルで処理した後、対応するアミン化合物と反応させることにより、化合物(2)を得ることができる。また、中間体(1)を対応するイソシアネートと反応させることにより、化合物(2)を得ることもできる。更に、化合物(2)をフッ化水素酸あるいはフッ化テトラブチルアンモニウムにより脱シリル化することにより化合物(3)を得ることができる。これら反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式２



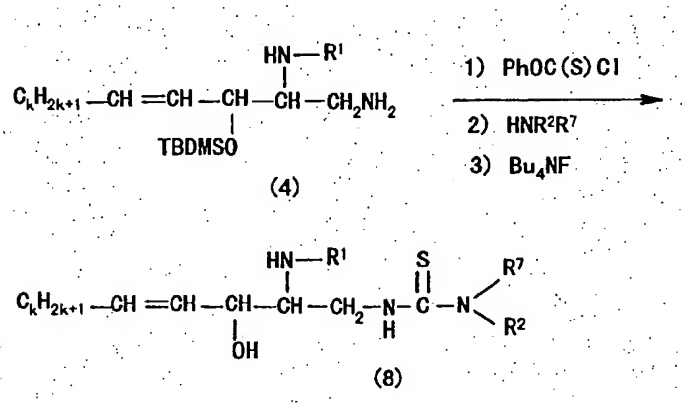
一般式（Ｉ）の化合物において、ＹがＮＨでありＷが酸素原子でありＺがＮＲ^{7}である化合物(7)は、式４に示した方法により製造することができる。すなわち、化合物(1)を、ジメチルスルホキシド中、三酸化硫黄ピリジン錯体及びトリエチルアミンで酸化しアルデヒド体とした後、ヒドロキシルアミン及び無水酢酸と順次反応させ、生成したアセトキシイミン体を水素化ホウ素ナトリウムにより還元しアミン化合物(4)へ変換した。なお、式３においては水酸基の保護基としてＴＢＤＭＳを用いた例を示しているが、前述の他の保護基を用いることにより、あるいは慣用の条件で脱保護することにより、他のアミン化合物を製造することができる。次いで化合物(4)を、クロロぎ酸フェニルあるいは二炭酸ジ-tert-ブチルで処理した後、対応するアミン化合物と反応させることにより、化合物(6)を得ることができる。また、化合物(4)を対応するイソシアネートと反応させることにより、化合物(6)を得ることもできる。更に、化合物(6)を脱シリル化することにより化合物(7)を得ることができる。これら反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式4



一般式（Ｉ）の化合物において、ＹがＮＨでありＷが硫黄原子でありＺがＮＲ^{7}である化合物(8)は、式５に示した方法により製造することができる。すなわち、化合物(4)を、クロロチオノぎ酸フェニルと反応後、対応するアミン化合物と反応させるか、あるいは対応するイソチオシアネートと反応させ、更に脱シリル化することにより化合物(8)を得ることができる。これら反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

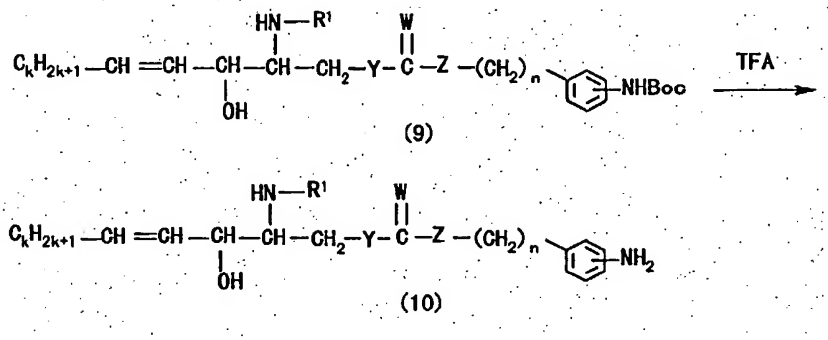
式５



一般式（Ｉ）の化合物において、Ｒ^{2}が式－(ＣＨ$_{2}$)$_{n}$Ｒ^{5}（Ｒ^{5}はアミノ基又はＣ

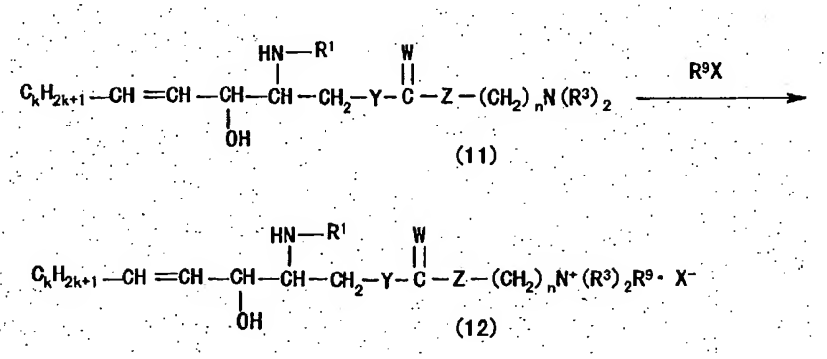
$_{2-5}$アルカノイルアミノ基で置換されたフェニル基）で示される基である化合物(10)及び化合物(11)は、式６に示した方法により製造することができる。すなわち、前記式２～５で示されるいずれかの方法で得られた化合物(9)をトリフルオロ酢酸によりBocを除去して化合物(10)を得る。アセチルアミノ基とする場合は、更に無水酢酸と反応させることによって化合物(11)へ変換することができる。これら反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式６



一般式（Ｉ）の化合物において、Ｒ^{2}が式－（ＣＨ$_{2}$）$_{n}$Ｒ^{5}（Ｒ^{5}は４級アミン）で示される基である化合物(13)は、式７に示した方法により製造することができる。すなわち、前記式２～５で示されるいずれかの方法で得られた化合物(12)を対応するハロゲン化アルキルと反応させることにより、化合物(13)を得ることができる。この反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式７

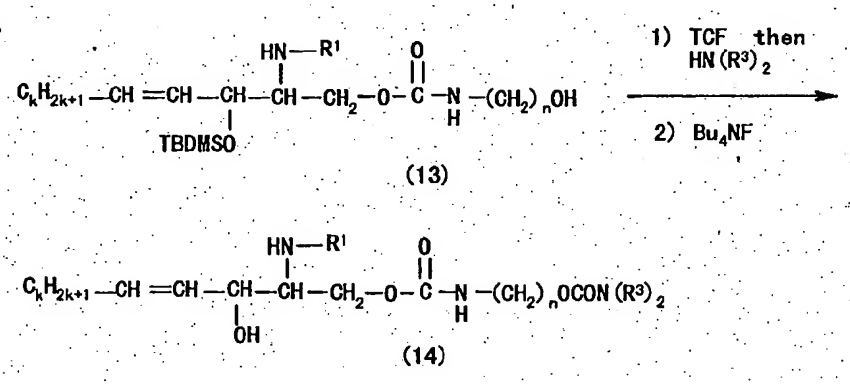


（式中、Ｒ^{9}はＣ$_{1-5}$アルキル基を示し、Ｘはハロゲン原子を示す。）

一般式（Ｉ）の化合物において、Ｒ^{2}が式－（ＣＨ$_{2}$）$_{n}$Ｒ^{5}（Ｒ^{5}はカルバモイルオ

キシ基又はC1-5アルキル基の1若しくは2個で置換されたアミノカルボニルオキシ基）で示される基である化合物(15)は、式8で示した方法で製造することができる。すなわち、前記式2～5で示されるいずれかの方法で得られた化合物(14)をクロロぎ酸トリクロロメチルで処理した後、対応するアミン化合物と反応させ、更に脱シリル化することにより化合物(15)を得ることができる。これらの反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

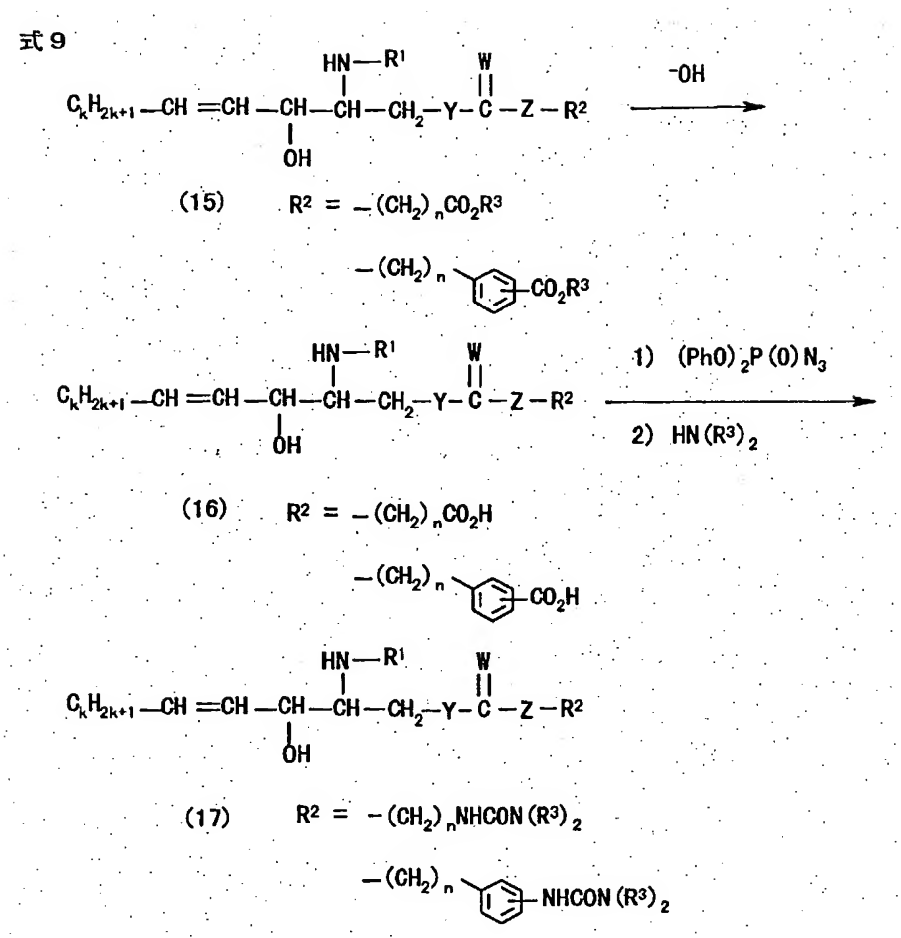
式8



一般式（Ｉ）の化合物において、Ｒ2が式－(ＣＨ2)nＲ5（Ｒ5はカルボキシル基又はカルボキシル基で置換されたフェニル基）で示される基である化合物(17)は、式9で示したように、前記式2～5で示されるいずれかの方法で得られた化合物(16)をエステルを加水分解する通常の方法により加水分解し得ることができる。

更に、化合物(17)をジフェニルリン酸アジドで処理した後、対応するアミン化合物と反応させることにより化合物(18)を得ることができる。これらの反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

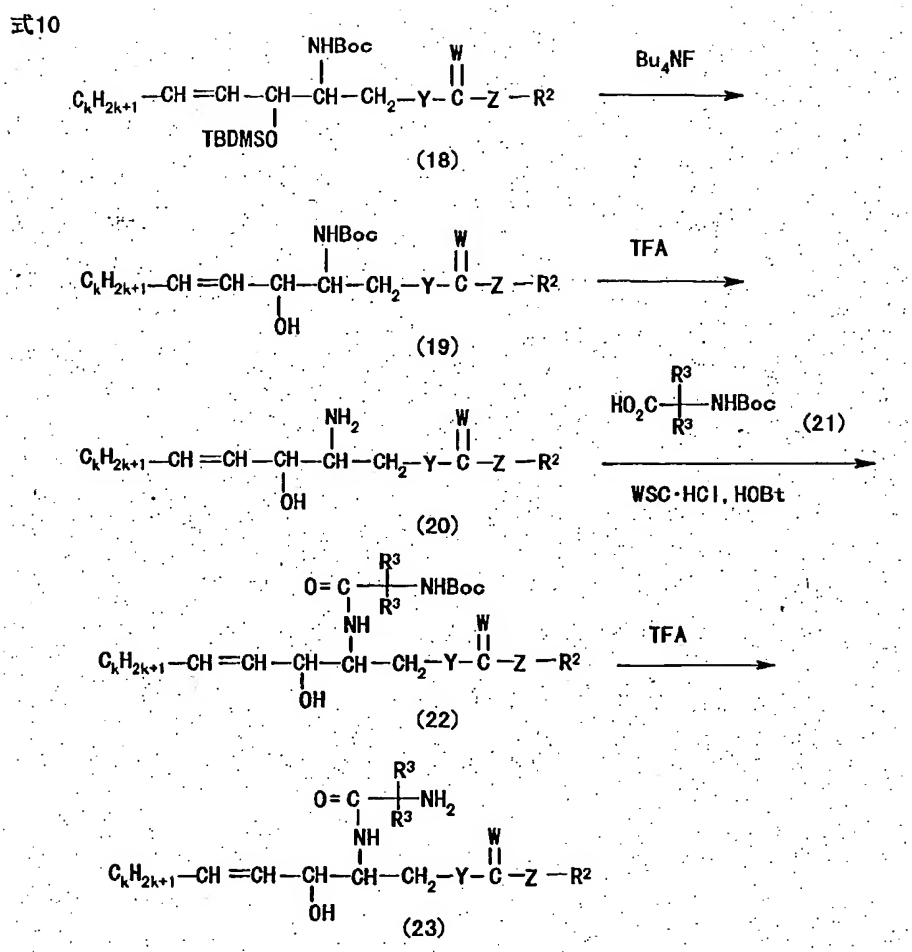
式９



式１０に示したように、N-Boc-スフィンゴシンより導かれる化合物(19)を脱シリル化することにより化合物(20)を得ることができる。次いで、ここで得られた化合物(20)をトリフルオロ酢酸で処理し、化合物(21)を得ることができる。

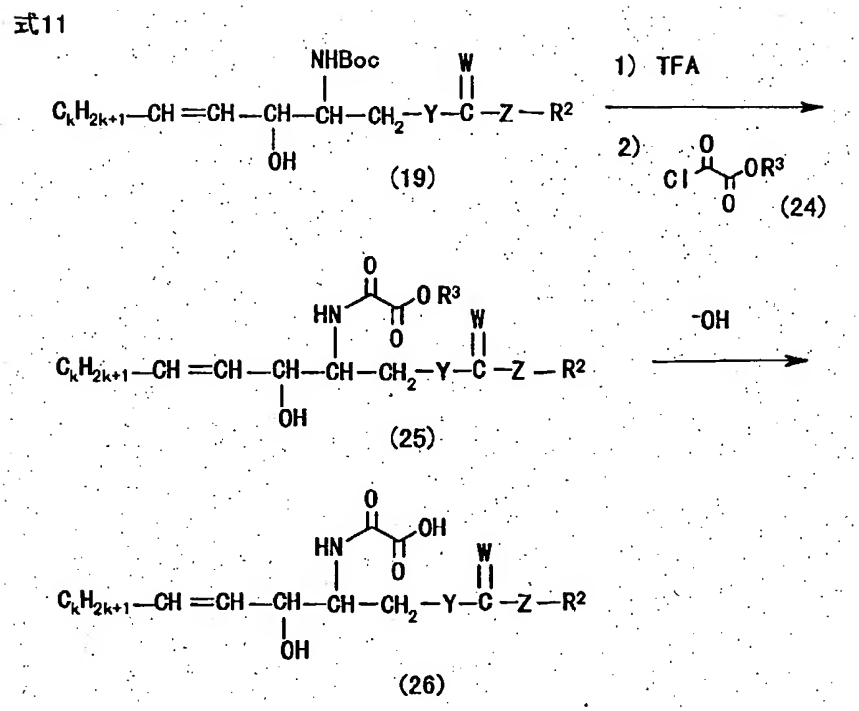
更に、化合物(21)とアミノ酸誘導体(22)とを縮合することにより、化合物(23)を得ることができる。化合物(23)はトリフルオロ酢酸で処理され、化合物(24)へ変換されることができる。これらの反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式10



また、式１１に示したように、化合物(21)を化合物(27)のハライドと反応させることにより、化合物(25)を得ることができる。更に、化合物(25)を加水分解することにより、化合物(26)へ変換できる。これらの反応での試薬、時間、温度及び溶媒等の反応条件は、通常用いられる条件で行うことができる。

式11



発明を実施するための最良の形態

以下、参考例、実施例及び試験例を挙げて本発明を更に詳細に説明する。

２－N－(tert－ブトキシカルボニル)－D－エリスロ－スフィンゴシンは文献記載の方法に準じて製造した（P.Herold,et al.,Helv.Chim.Acta.,1988,71,354）。

また、以下に記す^{1}Ｈ－ＮＭＲスペクトル値は、２００ＭＨｚで測定した(特に記載がない場合)。

参考例１

２－N－(tert－ブトキシカルボニル)－D－エリスロ－スフィンゴシン(5.6g,14mmol)のジクロロメタン(60ml)溶液へ、-20℃冷却下トリフルオロ酢酸(12ml)を滴下し、３時間かけて室温まで昇温した。溶媒を留去し、残留物に含水メタノール(水:メタノール＝12ml:200ml)、次いで炭酸カリウム(3.8g)を加えた後、室温で24時間撹拌した。溶媒を留去後、残留物をカラムクロマトグラフィーにより精製し、D－エリスロ－スフィンゴシン(5.5g)を得た。

ここで得られた化合物をテトラヒドロフラン(60ml)に溶解し、氷冷下トリエチルアミン(5.1ml,37mmol)を加え、次いで塩化ピバロイル(1.8ml,15mmol)を滴下した。

同温度下１時間攪拌した後、反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。抽出液を硫酸マグネシウムで乾燥後、溶媒を留去し残留物をカラムクロマトグラフィーで精製し、２-N-ピバロイル-D-エリスロ-スフィンゴシン(3.4g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.08-1.47(m,22H),1.21(s,9H),1.95-2.13(m,2H),2.83-3.07(m,2H),3.69(m,1H),3.78-4.02(m,2H),4.29(m,1H),5.51(dd,J=6.5,15.4Hz,1H),5.77(dt,J=15.4,6.9Hz,1H),6.42(d,J=6.8Hz,1H)

参考例２

参考例１で得られた化合物(0.90g,2.3mmol)をピリジン(8ml)に溶かし、-10℃冷却下、塩化ピバロイル(0.35ml)を滴下し、同温度下３時間攪拌した。反応液に水を加えた後、酢酸エチルで抽出し、硫酸マグネシウムで乾燥した。溶媒を留去し、残留物をカラムクロマトグラフィーで精製し、２-N,１-O-ジピバロイル-D-エリスロ-スフィンゴシン(0.90g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.19(s,9H),1.20(s,9H),1.23-1.42(m,22H),1.99-2.10(m,2H),3.09(bs,1H),4.14(dd,J=3.9,11.4Hz,1H),4.17(m,1H),4.24(m,1H),4.34(dd,J=7.0,11.4Hz,1H),5.46(ddt,J=6.6,15.4,1.3Hz,1H),5.75(ddt,J=0.9,15.4,1.3Hz,1H),6.09(d,J=7.6Hz,1H)

参考例３

参考例２で得られた化合物(2.3g,5.0mmol)をＮ,Ｎ-ジメチルホルムアミド(10ml)に溶かし、イミダゾール(2.72g,10mmol)を加え、次いでtert-ブチルジメチルシリルクロリド(2.7g,18mmol)を加え、60℃にて17時間攪拌した。反応液を減圧にて濃縮した後、残留物をカラムクロマトグラフィーで精製し、３-O-(tert-ブチルジメチルシリル)-２-N,１-O-ジピバロイル-D-エリスロ-スフィンゴシン(2.8g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.01(s,3H),0.04(s,3H),0.88(t,J=6.7Hz,3H),0.88(s,9H),1.15(s,9H),1.16(s,9H),1.22-1.38(m,22H),1.93-2.04(m,2H),3.29(dd,J=4.6,9.0Hz,1H),3.63(dd,J=3.6,9.0Hz,1H),3.91(m,1H),4.17(dd,J=6.7,7.4Hz,1H),5.42(dd,J=7.4,15.4Hz,1H),5.57(dt,J=15.4,6.7Hz,1H),5.91(d,J=8.6Hz,1H)

参考例４

参考例３で得られた生成物(2.8g,4.8mmol)を無水メタノール(30ml)に溶かし、１，８-ジアザビシクロ[５．４．０]ウンデセ-７-エン(0.68g,4.5mmol)を加え、室温で３日間攪拌した。反応液を減圧にて濃縮し、残留物をカラムクロマトグラフィーで精製し、３-O-(tert-ブチルジメチルシリル)-２-N-ピバロイル-D-エリスロ-スフィンゴシン(2.2g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.03(s,3H),0.06(s,3H),0.87(t,J=6.5Hz,3H),0.90(s,9H),1.02-1.44(m,22H),1.15(s,9H),1.93-2.11(m,2H),3.42(d,J=9.8Hz,1H),3.56(ddd,J=3.0,9.8,11.0Hz,1H),3.76(m,1H),4.00(dd,J=2.3,11.0Hz,1H),4.42(m,1H),5.44(dd,J=6.3,15.4Hz,1H),5.76(dt,J=15.4,6.6Hz,1H),6.52(d,J=7.0Hz,1H)

参考例５

２-N-(tert-ブトキシカルボニル)-D-エリスロ-スフィンゴシン(2.0g,5.0mmol)をピリジン(20ml)に溶かし、-20℃冷却下、塩化ピバロイル(0.66g,5.5mmol)を滴下した。反応液を２時間かけて室温まで戻した後、飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。抽出液を硫酸マグネシウムで乾燥後、溶媒を留去し、残留物をカラムクロマトグラフィーで精製し、２-N-(tert-ブトキシカルボニル)-１-O-ピバロイル-D-エリスロ-スフィンゴシン(2.2g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.21(s,9H),1.21-1.41(m,22H),1.44(s,9H),2.00-2.08(m,2H),2.33(bs,1H),3.94(m,1H),4.12(dd,J=4.4,11.4Hz,1H),4.15(m,1H),4.26(dd,J=6.6,11.4Hz,1H),4.80(bd,J=7.8Hz,1H),5.49(dd,J=6.8,15.4Hz,1H),5.75(dt,J=15.4,6.8Hz,1H)

参考例６

トリフルオロ酢酸(14ml)へ氷冷下、参考例5で得られた化合物(2.2g,4.5mmol)を加え、３時間かけて室温まで昇温した。減圧にて反応液を濃縮した後、エタノールを加え、再び濃縮した。残留物をテトラヒドロフラン(14ml)に溶かし、氷冷下トリエチルアミン(1.4g,14mmol)を加え、次いでイソ酪酸無水物(0.85g,5.4mmol)を加え、同温度下１．５時間攪拌した。反応液に水を加えた後、酢酸エチルで抽出した。抽出液を硫酸ナトリウムで乾燥した後、濃縮した。残留物をN,N-ジメチルホルムアミド(14ml)に溶かし、イミダゾール(1.6g,24mmol)を加え、次いでtert-ブチル

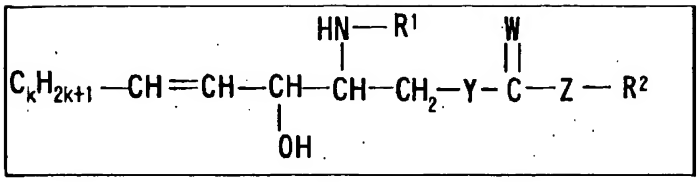
ジメチルシリルクロリド(1.2g,8.1mmol)を加え、室温で８時間攪拌し、反応液を減圧下濃縮後、水を加え、酢酸エチルで抽出した。硫酸ナトリウムで乾燥後、溶媒を留去し、残留物をカラムクロマトグラフィーで精製し、３-O-(tert-ブチルジメチルシリル)-２-N-イソブチリル-１-O-ピバロイル-D-エリスロ-スフィンゴシン(2.3g)を得た。

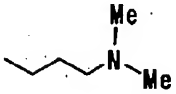
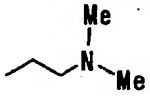
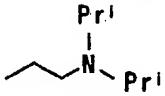
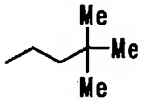
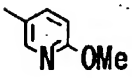
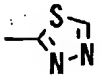
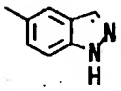
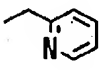
ここで得られた化合物(2.3g,4.0mmol)を脱水メタノール(30ml)に溶かし、１,８-ジアザビシクロ[５.４.０]ウンデセ-７-エン(0.92g,6.4mmol)を加え、室温で28時間攪拌した。反応液を減圧にて濃縮し、残留物をカラムクロマトグラフィーで精製し、３-O-(tert-ブチルジメチルシリル)-２-N-イソブチリル-D-エリスロ-スフィンゴシン(1.9g)を得た。

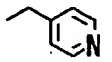
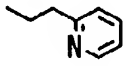
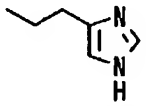
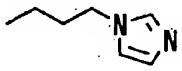
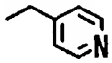
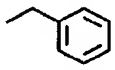
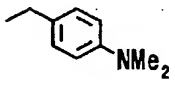
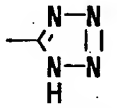
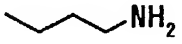
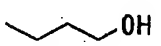
^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.02(s,3H),0.05(s,3H),0.85(t,J=6.7Hz,3H),0.89(s,9H),1.13(d,J=6.8Hz,6H),1.08-1.44(m,22H),1.94-2.14(m,2H),2.38(m,1H),3.31(m,1H),3.54(m,1H),3.77(m,1H),4.01(dd,J=3.0,11.3Hz,1H),4.42(dd,J=2.9,6.0Hz,1H),5.44(dd,J=6.2,15.4Hz,1H),5.71(dt,J=15.4,6.8Hz,1H),6.29(d,J=7.4Hz,1H)

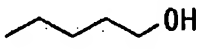
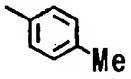
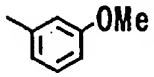
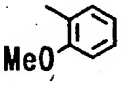
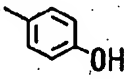
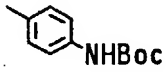
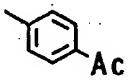
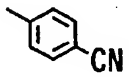
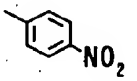
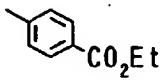
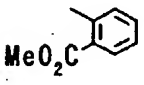
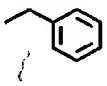
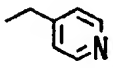
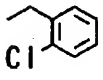
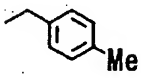
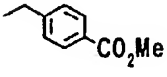
以下の実施例１から実施例１０４で製造した本発明の化合物を以下の表に示した。

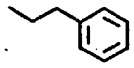
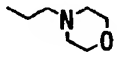
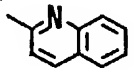
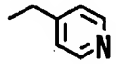
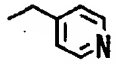
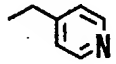
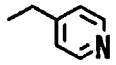
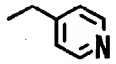
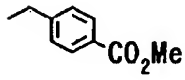
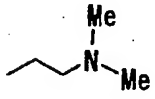
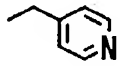
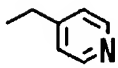
表1

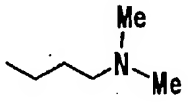
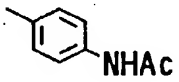
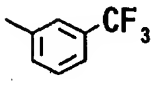
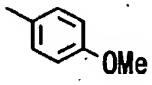
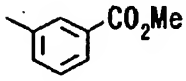
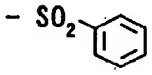
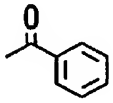
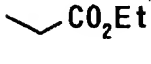
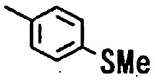
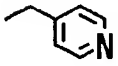
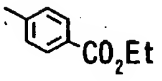


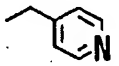
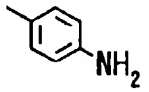
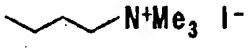
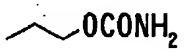
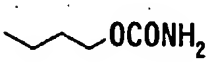
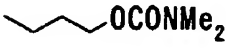
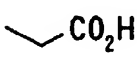
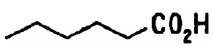
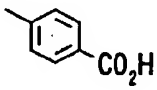
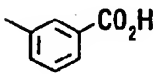
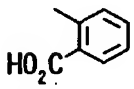
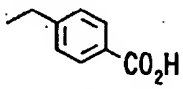
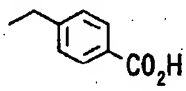
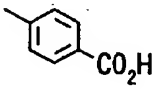
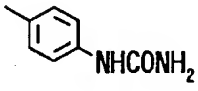
実施例	k	R^1	R^2	Y	Z	W
1	13	tBuCO	H	O	NH	O
2	13	tBuCO	OH	O	NH	O
3	13	tBuCO		O	NH	O
4	13	tBuCO		O	NH	O
5	13	tBuCO		O	NH	O
6	13	tBuCO		O	NH	O
7	13	tBuCO		O	NH	O
8	13	tBuCO		O	NH	O
9	13	tBuCO		O	NH	O
10	13	tBuCO		O	NH	O
11	13	tBuCO		O	NH	O
12	13	tBuCO		O	NH	O
13	13	tBuCO		O	NH	O
14	13	tBuCO		O	NH	O

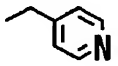
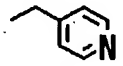
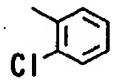
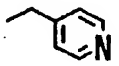
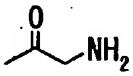
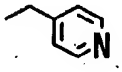
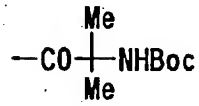
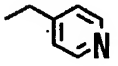
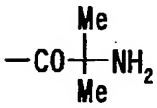
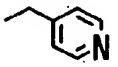
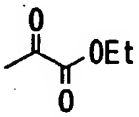
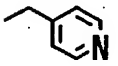
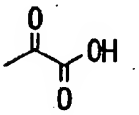
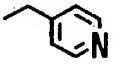
実施例	k	R^1	R^2	Y	Z	W
15	13	tBuCO		O	NH	O
16	13	tBuCO		O	NH	O
17	13	tBuCO		O	NH	O
18	13	tBuCO		O	NH	O
19	13	PhCO		O	NH	O
20	13	tBuCO		O	NH	O
21	13	tBuCO		O	NH	O
22	13	tBuCO		O	NH	O
23	13	tBuCO		O	NH	O
24	13	tBuCO		O	NH	O
25	13	tBuCO		O	NH	O
26	13	tBuCO		O	NH	O
27	13	tBuCO		O	NH	O
28	13	iPrCO	H	O	NH	O
29	13	iPrCO		O	NH	O
30	13	iPrCO		O	NH	O

実施例	k	R^1	R^2	Y	Z	W
31	13	iPrCO		O	NH	O
32	13	iPrCO		O	NH	O
33	13	iPrCO		O	NH	O
34	13	iPrCO		O	NH	O
35	13	iPrCO		O	NH	O
36	13	iPrCO		O	NH	O
37	13	iPrCO		O	NH	O
38	13	iPrCO		O	NH	O
39	13	iPrCO		O	NH	O
40	13	iPrCO		O	NH	O
41	13	iPrCO		O	NH	O
42	13	iPrCO		O	NH	O
43	13	iPrCO		O	NH	O
44	13	iPrCO		O	NH	O
45	13	iPrCO		O	NH	O
46	13	iPrCO		O	NH	O

実施例	k	R^1	R^2	Y	Z	W
47	13	iPrCO		O	NH	O
48	13	iPrCO		O	NH	O
49	13	iPrCO		O	NH	O
50	13	iPrCO		O	NH	O
51	13	iPrCO		O	NOH	O
52	1	$C_{13}H_{27}CO$		O	NH	O
53	6	iPrCO		O	NH	O
54	6	$C_{17}H_{35}CO$		O	NH	O
55	10	iPrCO		O	NH	O
56	10	iPrCO		O	NH	O
57	10	iPrCO	H	O	NH	O
58	10	iPrCO		O	NH	O
59	15	tBuCO		O	NH	O
60	15	tBuCO	H	O	NH	O
61	13	$C_{17}H_{35}CO$		O	NH	O
62	13	MeCO	H	O	NH	O

実施例	k	R^1	R^2	Y	Z	W
63	13	tBuCO		O	NMe	O
64	13	iPrCO		O	NH	O
65	13	iPrCO	Me	O	NH	O
66	13	iPrCO		O	NH	O
67	13	iPrCO		O	NH	O
68	13	iPrCO		O	NH	O
69	13	iPrCO		O	NH	O
70	13	iPrCO		O	NH	O
71	13	tBuCO		O	NH	O
72	13	tBuCO		O	NH	O
73	13	iPrCO		O	NH	O
75	13	tBuCO		NH	NH	O
76	13	tBuCO	H	NH	NH	O
77	13	tBuCO	Me	NH	NH	O
78	13	tBuCO		NH	NH	O

実施例	k	R^1	R^2	Y	Z	W
79	13	tBuCO		NH	NH	S
80	13	iPrCO		O	NH	O
81	13	tBuCO		O	NH	O
82	13	tBuCO		O	NH	O
83	13	tBuCO		O	NH	O
84	13	iPrCO		O	NH	O
85	13	tBuCO		O	NH	O
86	13	tBuCO		O	NH	O
87	13	iPrCO		O	NH	O
88	13	iPrCO		O	NH	O
89	13	iPrCO		O	NH	O
90	13	iPrCO		O	NH	O
91	10	iPrCO		O	NH	O
92	13	tBuCO		NH	NH	O
93	13	tBuCO		NH	NH	O
94	13	Boc	H	O	NH	O

実施例	k	R^1	R^2	Y	Z	W
95	13	Boc		O	NH	O
96	13	H	H	O	NH	O
97	13	H		O	NH	O
98	13	H		O	NH	O
99	13			O	NH	O
100	13			O	NH	O
101	13			O	NH	O
102	13			O	NH	O
103	13			O	NH	O
104	13			O	NH	O

実施例１

３－Ｏ－(tert－ブチルジメチルシリル)－２－Ｎ－ピバロイル－Ｄ－エリスロ－スフィンゴシン(99mg,0.2mmol)をジクロロメタン(５ml)に溶かしピリジン(142mg,1.8mmol)を加え、-78℃に冷却した。この溶液にクロロぎ酸トリクロロメチル(22μl,0.3mmol)を滴下した後、１時間かけて-15℃まで昇温した。この反応液に、25％アンモニア水(２ml)を滴下し、３時間かけて15℃まで昇温した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥した後、溶媒を留去した。残留物を

カラムクロマトグラフィーで精製し、3-O-(tert-ブチルジメチルシリル)-1-O-カルバモイル-2-N-ピバロイル-D-エリスロ-スフィンゴシン(72mg)を得た。

ここで得られた化合物(72mg,0.13mmol)をピリジン(6ml)に溶かし、氷冷下2%フッ化水素酸のアセトニトリル(34ml)溶液を加えた後、室温で7日間撹拌した。反応液に飽和炭酸水素ナトリウム水を加え、次いで酢酸エチルで抽出した後、硫酸マグネシウムで乾燥した。溶媒を留去し、残留物をカラムクロマトグラフィーで精製し、1-O-カルバモイル-2-N-ピバロイル-D-エリスロ-スフィンゴシン(51mg)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.19(s,9H),1.21-1.40(m,22H),2.03(m,2H),3.34(d,J=5.1Hz,1H),4.10(dd,J=3.8,11.8Hz,1H),4.14(m,1H),4.21(m,1H),4.41(dd,J=7.6,11.7Hz,1H),4.74(bs,2H),5.45(dd,J=6.7,15.4Hz,1H),5.74(dt,J=15.4,6.7Hz,1H),6.29(d,J=7.5Hz,1H)

MS(SIMS) m/e：427$(M+H)^+$ $C_{24}H_{46}N_2O_4$(426)

実施例2～63

実施例1の方法と同様にして実施例2～63の化合物を製造した。各化合物の^{1}H－NMRスペクトル、マススペクトル等の物理化学データーを以下に示す。

実施例2の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.19(s,9H),1.20-1.43(m,22H),2.04(m,2H),2.71(d,J=4.5Hz,1H),4.19(d,J=5.3Hz,1H),4.24(m,1H),4.30(dd,J=3,6,11.5Hz,1H),4.43(dd,J=7.8,11.6Hz,1H),5.47(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz,1H),6.05(bs,1H),6.21(d,J=7.8Hz,1H),7.19(bs,1H)

MS(SIMS)m/e：505 $(M+Na)^+$ $C_{28}H_{48}O_4$(504)

実施例3の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=7.0Hz,3H),1.17(s,9H),1.20-1.42(m,22H),1.90-2.08(m,4H),2.93(s,6H),3.16-3.34(m,4H),4.14(m,2H),4.30(m,1H),5.44(dd,J=6.7,15.3Hz,1H),5.77(dt,J=15.3,6.7Hz,1H),6.05(m,1H),6.32(d,J=8.0Hz,1H)

MS(SIMS)m/e：512 $(M+H)^+$ $C_{29}H_{57}N_3O_4$(511)

実施例4の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,1H),1.20(s,9H),1.22-1.40(m,22H),2.03(m,2H),2.82(s,6H),3.14(m,2H),3.45(m,1H),3.57(m,1H),4.12-4.34(m,2H),5.49(dd,J=6.4,15.3Hz,1H),5.78(dt,J=15.3,6.7Hz,1H),5.92(m,1H),6.47(d,J=7.6Hz,1H)

MS(SIMS)m/e：498 $(M+H)^+$ $C_{28}H_{55}N_3O_4$(497)

実施例5の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.88(t,J=6.7Hz,3H),1.01(d,J=6.4Hz,12H),1.18(s,9H),1.20-1.40(m,22H),2.02(m,2H),2.58(m,2H),3.01(m,2H),3.15(m,2H),3.78(m,1H),4.01-4.26(m,3H),4.42(dt,J=6.7,11.8Hz,1H),5.44(dd,J=6.6,15.4Hz,1H),5.72(dt,J=15.3,6.7Hz,1H)

MS(SIMS)m/e：554 $(M+H)^+$ $C_{32}H_{63}N_3O_4$(553)

実施例6の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),0.92(s,9H),1.19(s,9H),1.20-1.40(m,22H),1.41(m,2H),2.02(m,2H),3.05-3.25(m,2H),3.68(d,J=5.5Hz,1H),3.95-4.30(m,3H),4.42(dd,J=7.4,11.7Hz,1H),4.70(m,1H),5.44(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.41(d,J=7.1Hz,1H)

MS(SIMS)m/e：511 $(M+H)^+$ $C_{30}H_{58}N_2O_4$(510)

実施例7の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.5Hz,3H),1.17(s,9H),1.20-1.42(m,22H),2.02(m,2H),3.19(m,1H),4.19(m,1H),4.22-4.32(m,2H),4.52(dd,J=8.0,12.7Hz,1H),5.49(dd,J=6.7,15.4Hz,1H),5.76(dt,J=15.3,6.8Hz,1H),6.22(d,J=7.4Hz,1H),7.02(m,1H),7.70(m,1H),7.94(m,1H),8.13(bs,1H),8.27(m,1H)

MS(SIMS)m/e：504$(M+H)^+$ $C_{29}H_{49}N_3O_4$(503)

実施例8の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.04(m,2H),4.21(m,1H),4.27-4.35(m,2H),4.52(dd,J=8.2,12.4Hz,1H),5.50(dd,J=6.7,15.4Hz,1H),5.78(dt,J=15.4,6.5Hz,1H),6.17(d,J=7.8Hz,1H),7.45(bs,1H),8.22(m,1H),8.32(m,1H),9.29(m,1H)

MS(SIMS)m/e：505 $(M+H)^+$ $C_{28}H_{48}N_4O_4$(504)

実施例９の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),4.15-4.40(m,3H),4.50(dd,J=7.5,10.9Hz,1H),5.49(dd,J=6.5,15.4Hz,1H),5.78(dt,J=15.4,6.6Hz,1H),6.19(d,J=7.7Hz,1H),7.35(d,J=6.3Hz,1H),7.48(s,1H),8.47(d,J=6.3Hz,1H)

ＭＳ(SIMS)m/e：504 $(M+H)^+$ $C_{29}H_{49}N_3O_4$(503)

実施例１０の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=7.1Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),3.91(s,3H),4.12-4.33(m,3H),4.50(dd,J=4.7,12.4Hz,1H),5.47(dd,J=6.5,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.25(bd,J=6.2Hz,1H),6.73(d,J=8.9Hz,1H),6.78(bs,1H),7.75(bs,1H),8.09(bs,1H)

ＭＳ(SIMS)m/e：534 $(M+H)^+$ $C_{29}H_{49}N_3O_4$(533)

実施例１１の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.82(d,J=4.1Hz,1H),4.27(m,2H),4.43(dd,J=2.6,11.2Hz,1H),4.62(dd,J=3.6,11.1Hz,1H),5.54(J=6.3,15.3Hz,1H),5.78(dt,J=15.4,6.7Hz,1H),6.47(d,J=7.6Hz,1H),8.77(s,1H),12.2(bs,1H)

ＭＳ(SIMS)m/e：511$(M+H)^+$ $C_{26}H_{46}N_4O_4S$(510)

実施例１２の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),3.12(d,J=3.1Hz,1H),4.20(m,1H),4.22(dd,J=3.9,11.8Hz,1H),4.31(m,1H),4.53(dd,J=7.7,11.7Hz,1H),5.49(dd,J=6.6,15.4Hz,1H),5.77(dt,J=15.3,6.7Hz,1H),6.28(d,J=7.2Hz,1H),6.93(bs,1H),7.30(d,J=8.5Hz,1H),7.45(d,J=8.9Hz,1H),7.86(bs,1H),8.03(s,1H),10.1(bs,1H)

ＭＳ(SIMS)m/e：543$(M+H)^+$ $C_{31}H_{50}N_4O_4$(542)

実施例１３の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.16(s,9H),1.20-1.40(m,22H),2.01(m,2H),4.12(m,2H),4.19(m,1H),4.43-4.54(m,3H),5.45(dd,J=6.7,15.4Hz,1H),5.72(dt,

J=15.4,6.7Hz,1H),5.96(m,1H),6.36(d,J=7.1Hz,1H),7.18-7.30(m,2H),7.68(m,1H),8.55(m,1H)

MS(SIMS)m/e：518$(M+H)^+$ $C_{30}H_{51}N_3O_4$(517)

実施例１４の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-1.40(m,22H),2.02(m,2H),4.13(m,2H),4.21(m,1H),4.38(m,2H),4.43(dd,J=7.7,11.6Hz,1H),5.38(m,1H),5.45(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.7Hz,1H),6.28(d,J=7.4Hz,1H),7.29(m,1H),7.65(m,1H),8.55(m,2H)

MS(SIMS)m/e：518$(M+H)^+$ $C_{30}H_{51}N_3O_4$(517)

実施例１５の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.5Hz,3H),1.15(s,9H),1.20-1.44(m,22H),2.02(m,2H),3.72(m,1H),4.13-4.17(m,3H),4.34-4.48(m,3H),5.45(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.3,6.6Hz,1H),6.29(d,J=7.4Hz,1H),7.20(m,2H),8.57(m,2H)

MS(SIMS)m/e：518$(M+H)^+$ $C_{30}H_{51}N_3O_4$(517)

実施例１６の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.01(m,2H),2.97(m,2H),3.61(m,2H),4.06(m,2H),4.16(m,1H),4.42(dd,J=7.3,11.9Hz,1H),5.43(dd,J=6.6,15.3Hz,1H),5.71(dt,J=15.4,6.6Hz,1H),6.39(d,J=7.2Hz,1H),7.16(m,2H),7.62(m,1H),8.53(m,1H)

MS(SIMS)m/e：532$(M+H)^+$ $C_{31}H_{53}N_3O_4$(531)

実施例１７の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.20(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.82(m,2H),3.37(m,1H),3.52(m,1H),4.10-4.37(m,4H),5.40(bs,1H),5.47(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.6,6.3Hz,1H),6.37(d,J=7.0Hz,1H),6.83(s,1H),7.59(s,1H)

MS(SIMS)m/e：521$(M+H)^+$ $C_{29}H_{52}N_4O_4$(520)

実施例１８の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.86(t,J=6.4Hz,3H),1.07-1.42(m,22H),1.15(s,9H),1.87-2.10(m,4H),3.02-3.23(m,3H),4.00(t,J=6.8Hz,2H),4.05-4.27(m,3H),4.37(dd,J=7.0,1

0.9Hz,1H),5.44(dd,J=6.3,15.4Hz,1H),5.62-5.82(m,2H),6.32(d,J=7.4Hz,1H),6.92(bs,1H),7.03(bs,1H),7.03(bs,1H),7.52(bs,1H)

MS(SIMS)m/e：535$(M+H)^+$ $C_{30}H_{54}N_4O_4$(534)

実施例19の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ (ppm)：0.81(t,J=6.5Hz,3H),0.96-1.40(m,22H),1.84-2.08(m,2H),4.02-4.50(m,6H),5.45(dd,J=6.4,15.5Hz,1H),5.71(dt,J=15.5,6.3Hz,1H),7.08(d,J=5.4Hz,2H),7.22-7.53(m,2H),7.71(d,J=6.9Hz,2H),8.28(d,J=5.4Hz,2H)

MS(SIMS)m/e：538$(M+H)^+$ $C_{32}H_{47}N_3O_4$(537)

実施例20の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.16(s,9H),1.22-1.40(m,22H),2.02(m,2H),3.56(bs,1H),4.11(m,2H),4.20(m,1H),4.36(m,2H),4.45(dd,J=7.6,11.8Hz,1H),5.16(m,1H),5.44(dd,J=6.6,15.3Hz,1H),5.72(dt,J=15.4,6.6Hz,1H),6.37(d,J=7.0Hz,1H),7.26-7.40(m,5H)

MS(SIMS)m/e：517$(M+H)^+$ $C_{31}H_{52}N_2O_4$(516)

実施例21の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.17(s,9H),1.22-1.40(m,22H),2.02(m,2H),2.94(s,6H),3.69(d,J=5.1Hz,1H),4.08(m,2H),4.19(m,1H),4.25(m,2H),4.45(dd,J=7.4,11.9Hz,1H),5.00(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.71(dt,J=15.3,6.5Hz,1H),6.40(d,J=7.0Hz,1H),6.69(d,J=8.5Hz,2H),7.14(d,J=8.5Hz,2H)

MS(SIMS)m/e：582$(M+Na)^+$ $C_{33}H_{57}N_3O_4$(559)

実施例22の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.13-1.44(m,22H),1.17(s,9H),1.19-2.11(m,2H),3.15-3.43(m,2H),3.35(bs,1H),3.60-3.82(m,2H),4.06-4.36(m,4H),5.44(dd,J=6.3,15.4Hz,1H),5.62(t,J=5.7Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.34(d,J=5.8Hz,1H)

MS(CI)m/e：471$(M+H)^+$ $C_{26}H_{50}N_2O_5$(471)

実施例23の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.19(s,9H),1.20-1.40(m,22H),1.

72(m,2H),2.03(m,2H),2.25(m,1H),3.32(m,1H),3.39(dd,J=5.0,16.1Hz,1H),3.71(m,2H),4.06-4.16(m,3H),4.39(dd,J=7.6,11.8Hz,1H),5.12(bs,1H),5.45(dd,J=6.6,15.4Hz,1H),5.73(dt,J=15.3,6.8Hz,1H),6.34(d,J=7.2Hz,1H)

MS(SIMS)m/e：485$(M+H)^+$ $C_{27}H_{52}N_2O_5$(484)

実施例２４の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.86(t,J=6.4Hz,3H),1.06-1.40(m,22H),1.19(s,9H),1.40-1.73(m,4H),1.92-2.08(m,2H),2.32(t,J=7.0Hz,2H),3.07-3.25(m,2H),3.66(s,3H),3.76(bs,1H),3.96-4.22(m,3H),4.40(m,1H),5.03(t,J=5.7Hz,1H),5.42(dd,J=6.3,15.4Hz,1H),5.70(dt,J=15.4,6.5Hz,1H),6.38(d,J=6.9Hz,1H)

MS(SIMS)m/e：541$(M+H)^+$ $C_{30}H_{56}N_2O_6$(540)

実施例２５の化合物

^{1}H－NMR(500MHz, $CDCl_3$-CD_3OD) δ (ppm)：0.85(t,J=6.3Hz,3H),1.08-1.42(m,22H),1.15(s,9H),1.19-2.12(m,2H),4.16-4.48(m,4H),5.46(dd,J=5.5,15.5Hz,1H),5.78(dt,J=15.5,6.5Hz,1H),6.51(bs,1H)

MS(SIMS)m/e：495$(M+H)^+$ $C_{25}H_{46}N_6O_4$(494)

実施例２６の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.46(m,2H),3.35(d,J=5.1Hz,1H),3.47(m,2H),4.06-4.22(m,3H),4.36(dd,J=7.0,11.7Hz,1H),5.35(bs,1H),5.41-5.54(m,2H),5.68(bs,1H),5.72(dt,J=15.4,6.4Hz,1H),6.25(d,J=7.1Hz,1H)

MS(SIMS)m/e：498$(M+H)^+$ $C_{27}H_{51}N_3O_5$(497)

実施例２７の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),1.75-1.92(m,2H),1.94-2.05(m,2H),2.90-3.03(m,2H),3.22(bs,2H),3.24-3.36(m,2H),3.65(d,J=4.3Hz,1H),4.00-4.25(m,3H),4.34(m,1H),5.44(dd,J=5.5,15.1Hz,1H),5.74(dt,J=15.1,5.9Hz,1H),6.11(bs,1H),6.37(d,J=6.4Hz,1H)

MS(SIMS)m/e：484$(M+H)^+$ $C_{27}H_{53}N_3O_4$(483)

実施例２８の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.88(t,J=6.4Hz,3H),1.15(d,J=6.9Hz,6H),1.15-1.47(m,22H),1.93-2.11(m,2H),2.37(m,1H),3.21(bs,1H),4.04-4.28(m,3H),4.42(dd,J=6.8,11.1Hz,1H),5.01(bs,2H),5.45(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.06(d,J=7.4Hz,1H)

MS(SIMS)m/e：413$(M+H)^+$ $C_{23}H_{44}N_2O_4$(412)

実施例２９の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.4Hz,3H),1.12-1.45(m,22H),1.15(d,J=7.0Hz,6H),1.94-2.12(m,2H),2.38(m,1H),2.74(bs,1H),3.00(d,J=4.5Hz,1H),3.15-3.47(m,2H),3.58-3.85(m,2H),4.08-4.32(m,4H),5.20(bs,1H),5.47(dd,J=6.3,15.4Hz,1H),5.75(dt,J=15.4,6.5Hz,1H),6.09(bs,1H)

MS(SIMS)m/e：457$(M+H)^+$ $C_{25}H_{48}N_2O_5$(456)

実施例３０の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.87(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.18-1.42(m,22H),1.60-1.80(m,2H),1.95-2.10(m,2H),2.37(m,1H),2.48(bs,1H),3.22-3.42(m,3H),3.70(t,J=5.6Hz,2H),4.04-4.27(m,3H),4.36(dd,J=6.6,10.9Hz,1H),5.21(bs,1H),5.45(dd,J=6.3,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.12(d,J=7.4Hz,1H)

MS(SIMS)m/e：471$(M+H)^+$ $C_{26}H_{50}N_2O_5$(470)

実施例３１の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.88(t,J=6.9Hz,3H),1.14(d,J=6.9Hz,6H),1.20-1.47(m,22H),1.59-1.86(m,4H),2.37(m,1H),2.98(m,1H),3.13-3.31(m,2H),3.60-3.75(m,2H),4.00-4.26(m,3H),4.39(dd,J=7.1,9.3Hz,1H),4.95(bs,1H),5.46(dd,J=6.7,15.4Hz,1H),5.75(dt,J=15.4,6.5Hz,1H),6.12(d,J=6.7Hz,1H)

MS(SIMS)m/e：485$(M+H)^+$ $C_{27}H_{52}N_2O_5$(484)

実施例３２の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.4Hz,3H),1.08-1.50(m,22H),1.97-2.14(m,2H),2.30(s,3H),2.62(m,1H),3.99(m,1H),4.22-4.44(m,2H),4.98(m,1H),5.48(dd,J=8.3,15.3Hz,1H),5.82(dt,J=15.3,6.6Hz,1H),6.64(s,1H),7.09(d,J=8.8Hz,2H),7.24(d,J=8.8Hz,2H)

MS(SIMS)m/e：503$(M+H)^+$ $C_{30}H_{50}N_2O_4$(502)

実施例33の化合物

^{1}H－NMR(500MHz, $CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.13(d,J=6.4Hz,3H),1.14(d,J=6.6Hz,3H),1.18-1.39(m,22H),1.96-2.08(m,2H),2.37(m,1H),3.08(bs,1H),3.80(s,3H),4.11-4.24(m,2H),4.24(m,1H),4.48(dd,J=7.3,11.6Hz,1H),5.49(dd,J=7.9,15.4Hz,1H),5.70(dt,J=15.4,6.7Hz,1H),6.07(d,J=8.0Hz,1H),6.63(m,1H),6.87(d,J=7.9Hz,1H),6.90(bs,1H),7.09(bs,1H),7.20(m,1H)

MS(SIMS)m/e：519$(M+H)^+$ $C_{30}H_{50}N_2O_5$(518)

実施例34の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.14(d,J=6.9Hz,3H),1.21-1.38(m,22H),2.00-2.08(m,2H),2.38(m,1H),3.25(bs,1H),3.87(s,3H),4.11-4.25(m,2H),4.28(m,1H),4.50(dd,J=7.0,11.7Hz,1H),5.49(dd,J=6.7,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.09(d,J=7.9Hz,1H),6.87(d,J=8.0Hz,1H),6.96(m,1H),7.02(m,1H),7.30(m,1H),8.05(bs,1H)

MS(SIMS)m/e：519$(M+H)^+$ $C_{30}H_{50}N_2O_5$(518)

実施例35の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1.87-2.05(m,2H),2.32(m,1H),3.99-4.36(m,4H),5.40(dd,J=6.2,15.4Hz,1H),5.68(dt,J=15.4,6.6Hz,1H),6.60(m,1H),6.70(d,J=8.7Hz,2H),7.12(d,J=8.7Hz,2H)

MS(CI)m/e：505$(M+H)^+$ $C_{29}H_{47}N_2O_5$(504)

実施例36の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.83(t,J=6.4Hz,3H),1.05(d,J=6.9Hz,3H),1.07(d,J=6.8Hz,3H),1.12-1.40(m,22H),1.46(s,9H),1.90-2.07(m,2H),2.33(m,1H),4.02-4.38(m,4H),5.41(dd,J=6.1,15.4Hz,1H),5.70(dt,J=15.4,6.6Hz,1H),6.56(d,J=7.8Hz,1H),6.90(bs,1H),7.24(s,4H)

MS(SIMS)m/e：504$(M+H)^+$ $C_{29}H_{49}N_3O_4$(503)

実施例37の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ (ppm)：0.82(t,J=6.4Hz,3H),1.04(d,J=6.6Hz,3H),1.07(d,J=6.6Hz,3H),1.05-1.41(m,22H),1.88-2.08(m,2H),2.33(m,1H),2.51(s,3H),4.05-4.40(m,4H),5.42(dd,J=6.2,15.4Hz,1H),5.71(dt,J=15.4,6.6Hz,1H),6.58(d,J=7.8Hz,1H),7.45(d,J=8.8Hz,2H),7.86(d,J=8.8Hz,2H)

MS(SIMS)m/e：531$(M+H)^+$ $C_{31}H_{50}N_2O_5$(530)

実施例３８の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ (ppm)：0.84(t,J=6.2Hz,3H),1.05(d,J=6.9Hz,3H),1.08(d,J=6.9Hz,3H),1.03-1.43(m,22H),1.09-2.09(m,2H),2.34(m,1H),4.07-4.38(m,4H),5.43(dd,J=6.1,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.49(d,J=6.3Hz,1H),7.40-7.65(m,4H)

MS(SIMS)m/e：514$(M+H)^+$ $C_{30}H_{47}N_3O_4$(513)

実施例３９の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.45(m,22H),1.88-2.10(m,2H),2.38(m,1H),2.86(bs,1H),4.15-4.55(m,4H),5.49(dt,J=15.5,6.3Hz,1H),5.77(dd,J=6.5,15.5Hz,1H),6.08(d,J=7.7Hz,1H),7.59(d,J=9.2Hz,2H),8.12(bs,1H),8.18(d,J=9.2Hz,2H)

MS(SIMS)m/e：534$(M+H)^+$ $C_{29}H_{47}N_3O_6$(533)

実施例４０の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.08-1.52(m,22H),1.10(d,J=6.8Hz,3H),1.12(d,J=6.8Hz,3H),1.37(t,J=7.1Hz,3H),1.90-2.11(m,2H),2.38(m,1H),4.14-4.57(m,4H),4.38(q,J=7.1Hz,2H),5.48(dd,J=6.3,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz,1H),6.15(d,J=7.8Hz,1H),7.46(d,J=8.7Hz,2H),7.73(bs,1H),7.98(d,J=8.7Hz,2H)

MS(SIMS)m/e：561$(M+H)^+$ $C_{32}H_{52}N_2O_6$(560)

実施例４１の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.87(t,J=6.4Hz,3H),1.05(d,J=6.7Hz,6H),1.02-1.47(m,22H),1.90-2.10(m,2H),2.39(m,1H),3.22(bs,1H),3.92(s,3H),4.13-4.23(m,3H),4.50(m,1H),5.50(dd,J=6.3,15.4Hz,1H),5.74(dt,J=15.4,6,5Hz,1H),6.05(d,J=7.2Hz,1H),7.06(m,1H),7.54(m,1H),8.02(dd,J=1.7,8.0Hz,1H),8.40(d,J=8.4Hz,1H),10.60(s,1H)

MS(SIMS)m/e：547$(M+H)^+$ $C_{31}H_{50}N_2O_6$(546)

実施例４２の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.48(m,22H),1.90-2.12(m,2H),2.34(m,1H),3.90-4.27(m,3H),4.34(d,J=5.8Hz,2H),4.42(m,1H),5.29(t,J=5.8Hz,1H),5.44(dd,J=6.3,15.5Hz,1H)5.71(dt,J=15.5,6.7Hz,1H),6.17(d,J=7.1Hz,1H),7.16-7.42(m,5H)

MS(CI)m/e503：$(M+H)^+$ $C_{30}H_{50}N_2O_4$(502)

実施例４３の化合物

^{1}H－NMR($CDCl_3$) δ (ppm):0.87(t,J=6.2Hz,3H),1.10(d,J=6.8Hz,6H),1.17-1,48(m,22H),1.89-2.11(m,2H),2.34(m,1H),4.08-4.29(m,3H),4.29-4.48(m,3H),5.45(dd,J=5.9,15.3Hz,1H),5.60(t,J=5.9Hz,1H),5.73(dt,J=15.3,6.7Hz,1H),6.12(d,J=6.9Hz,1H),7.19(d,J=5.3Hz,2H),8.54(d,J=5.3Hz,2H)

MS(SIMS)m/e：604$(M+H)^+$ $C_{34}H_{57}N_3O_6$(603)

実施例４４の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.17-1.45(m,22H),1.92-2.10(m,2H),2.32(m,1H),3.40(bs,1H),4.02-4.27(m,3H),4.40(m,1H),4.43(d,J=6.2Hz,2H),5.31-5.51(m,2H),5.70(dt,J=15.4,6.8Hz,1H),6.12(d,J=7.2Hz,1H),7.17-7.43(m,4H)

MS(CI)m/e：537 $(M+H)^+$ $C_{30}H_{49}ClN_2O_4$(536)

実施例４５の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ (ppm)：0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.45(m,22H),1.92-2.09(m,2H),2.33(s,3H),3.54(bs,1H),4.03-4.26(m,3H),4.29(d,J=5.7Hz,2H),4.41(dd,J=6.8,11.1Hz,1H),5.24(t,J=5.5Hz,1H),5.44(dd,J=6.2,15.4Hz,1H),5.71(dt,J=15.4,6.3Hz,1H),6.19(d,J=7.1Hz,1H),7.14(s,4H)

MS(SIMS)m/e：517$(M+H)^+$ $C_{31}H_{52}N_2O_4$(516)

実施例４６の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1,87-2.05(m,2H),2.32(m,1H),3.99-4.36(m,4H),5.40(dd,J=

6.2,15.4Hz,1H),5.68(dt,J=15.4,6.6Hz,1H),6.60(m,1H),6.70(d,J=8.7Hz,2H),7.12(d,J=8.7Hz,2H)

MS(SIMS)m/e：561$(M+H)^+$ $C_{32}H_{52}N_2O_6$(560)

実施例４７の化合物

^{1}H－NMR($CDCl_3$) δ(ppm):0.87(t,J=6.3Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.48(m,22H),1.91-2.12(m,2H),2.35(m,1H),2.80(t,J=7.0Hz,2H),3.31-3.56(m,3H),3.99-4.26(m,3H),4.38(dd,J=6.7,11.2Hz,1H),4.92(t,J=5.3Hz,1H),5.44(dd,J=6.3,15.4Hz,1H),5.71(dt,J=15.4,6.5Hz,1H),6.13(d,J=7.3Hz,1H),7.10-7.38(m,5H)

MS(CI)m/e：517$(M+H)^+$ $C_{31}H_{52}N_2O_4$(516)

実施例４８の化合物

^{1}H－NMR($CDCl_3$) δ(ppm):0.88(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.12-1.45(m,22H),1.93-2.11(m,2H),2.20-2.56(m,8H),3.18-3.38(m,2H),3.64-3.79(m,4H),4.01-4.28(m,3H),4.40(dd,J=6.4,15.4Hz,1H),5.73(dt,J=15.4,6.5Hz,1H),6.12(d,J=7.1Hz,1H)

MS(CI)m/e526$(M+H)^+$ $C_{29}H_{55}N_3O_5$(525)

実施例４９の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.83(t,J=6.6Hz,3H),1.05(d,J=6.7Hz,3H),1.07(d,J=6.7Hz,3H),1.05-1.45(m,22H),1.85-2.08(m,2H),2.33(m,1H),4.05-4.50(m,4H),5.42(dd,J=6.3,15.5Hz,1H),5.73(dt,J=15.5,6.7Hz,1H),6.57(d,J=8.0Hz,1H),6.87(d,J=3.5Hz,1H),7.31(d,J=3.5Hz,1H)

MS(CI)m/e：496$(M+H)^+$ $C_{26}H_{45}N_3O_4S$(495)

実施例５０の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.87(t,J=6.4Hz,3H),1.00-1.45(m,22H),1.11(d,J=6.8Hz,6H),1.90-2.10(m,2H),2.35(m,1H),3.05(bs,1H),4.14-4.38(m,3H),4.50(m,1H),5.50(dd,J=6.2,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz,1H),6.15(d,J=7.7Hz,1H),7.40(m,1H),7.65(m,1H),7.76(d,J=7.9Hz,1H),7.83(d,J=8.4Hz,1H),8.15(s,2H)

MS(CI)m/e：540$(M+H)^+$ $C_{32}H_{49}N_3O_4$(539)

実施例５１の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.88(t,J=7.0Hz,3H),1.07(d,J=6.9Hz,2H),1.09(d,J=6.

9Hz,2H),1.18-1.40(m,22H),1.97-2.09(m,2H),2.32(m,1H),4.13-4.25(m,2H),4.34(dd,J=3.2,11.6Hz,1H),4.41(dd,J=7.6,11.6Hz,1H),4.66(d,J=15.9Hz,1H),4.75(d,J=15.9Hz,1H),5.48 (dd,J=6.3,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.19(d,J=7.6Hz,1H),7.26(d,J=4.7Hz,2H),8.43(d,J=4.7Hz,2H)

MS(SIMS)m/e：520 $(M+H)^+$ $C_{29}H_{49}N_3O_5$(519)

実施例５２の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.20-1.36(m,20H),1.60(m,2H),1.71(d,J=6.4Hz,1H),2.17(m,2H),4.10-4.19(m,2H),4.21(m,1H),4.27(m,1H),4.35(d,J=2.9Hz,1H),5.49(m,1H),5.76(m,1H),6.28(bd,1H),6.38(bd,1H),7.23(d,J=5.6Hz,1H),8.53(d,J=5.3Hz,1H)

実施例５３の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.05-1.50(m,22H),1.90-2.16(m,2H),2.34(m,1H),3.98-4.52(m,6H),5.34-5.60(m,2H),5.73(dt,J=15.4,6.8Hz,1H),6.10(d,J=7.1Hz,1H),7.19(d,J=5.5Hz,1H),8.55(d,J=5.5Hz,1H)

MS(CI)m/e406$(M+H)^+$ $C_{22}H_{35}N_3O_4$(405)

実施例５４の化合物

^{1}H－NMR(500MHz, $CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,6H),1.18-1.40(m,34H),1.53-1.69(m,4H),1.96-2.10(m,2H),2.11-2.22(m,2H),3.07(bs,1H),4.11-4.20(m,2H),4.25(m,1H),4.34-4.44(m,3H),5.31(t,J=6.1Hz,1H),5.47(dd,J=6.6,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz,1H),6.01(d,J=8.0Hz,1H),7.20(d,J=5.8Hz,2H),8.57(d,J=5.8Hz,2H)

MS(SIMS)m/e：602$(M+H)^+$ $C_{36}H_{63}N_3O_4$(601)

実施例５５の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.10(d,J=6.8Hz,6H),1.12-1.47(m,16H),1.90-2.13(m,2H),2.33(m,1H),3.40(bs,1H),4.04-4.50(m,6H),5.44(dd,J=6.2,15.5Hz,1H),5.57-5.82(m,2H),6.14(d,J=7.3Hz,1H),7.23(d,J=5.8Hz,2H),8.53(d,J=5.8Hz,2H)

MS(SIMS)m/e：462$(M+H)^+$ $C_{26}H_{43}N_3O_4$(461)

実施例５６の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.3Hz,3H),1.10(d,J=6.7Hz,6H),1.10-1.46(m,

16H),1.90-2.10(m,2H),2.33(m,1H),3.35(bs,1H),3.90(s,3H),4.04-4.27(m,3H),4.31-4.51(m,3H),5.33-5.65(m,2H),5.72(dt,J=15.2,6.5Hz,1H),6.14(d,J=7.2Hz,1H),7.33(d,J=8.1Hz,2H),7.99(d,J=8.1Hz,2H)

MS(SIMS)m/e：519$(M+H)^+$ $C_{29}H_{46}N_2O_6$(518)

実施例57の化合物

^{1}H－NMR($CDCl_3$) δ(ppm):0.88(t,J=6.3Hz,3H),1.15(d,J=6.9Hz,6H),1.11-1.46(m,16H),1.94-2.13(m,2H),2.37(m,1H),3.17(bs,1H),4.06-4.29(m,3H),4.39(dd,J=6.8,11.1Hz,1H),4.74(bs,2H),5.45(dd,J=6.5,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz,1H),6.06(d,J=7.1Hz,1H)

MS(CI)m/e：371$(M+H)^+$ $C_{20}H_{38}N_2O_4$(370)

実施例58の化合物

^{1}H－NMR($CDCl_3$) δ(ppm):0.86(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.13-1.43(m,16H),1.90-2.08(m,2H),2.21(s,6H),2.36(m,1H),2.40(t,J=6.3Hz,2H),2.47(bs,1H),3.24(m,2H),4.00-4.23(m,3H),4.39(dd,J=6.0,11.1Hz,1H),5.44(dd,J=6.4,15.4Hz,1H),5.58(m,1H),5.71(dt,J=15.4,6.4Hz,1H),6.29(d,J=7.2Hz,1H)

MS(CI)m/e：442$(M+H)^+$ $C_{24}H_{47}N_3O_4$(441)

実施例59の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.88(t,J=6.6Hz,3H),1.19(s,9H),1.20-1.40(m,26H),2.03(m,2H),3.32(d,J=5.4Hz,1H),4.10(dd,J=3.8,11.9Hz,1H),4.14(m,1H),4.21(m,1H),4.41(dd,J=7.6,11.8Hz,1H),4.69(bs,2H),5.45(dd,J=6.7,15.4Hz,1H),5.74(dt,J=15.3,6.8Hz,1H),6.29(d,J=7.4Hz,1H)

MS(SIMS)m/e：455$(M+H)^+$ $C_{26}H_{50}N_2O_4$(454)

実施例60の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.88(t,J=6.8Hz,3H),1.15(s,9H),1.20-1.40(m,26H),2.02(m,2H),3.33(bs,1H),4.13(m,2H),4.20(m,1H),4.32-4.49(m,3H),5.25(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.28(d,J=7.4Hz,1H),7.28(m,1H),7.63(d,J=7.7Hz,1H),8.55(m,2H)

MS(SIMS)m/e：546$(M+H)^+$ $C_{32}H_{55}N_3O_4$(545)

実施例６１の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,6H),1.08-1.43(m,52H),1.93-2.10(m,2H),2.17(t,J=7.5Hz,2H),2.98(bs,1H),4.10-4.44(m,6H),5.34(t,J=6.3Hz,1H),5.47(dd,J=6.6,15.6Hz,1H),5.74(dt,J=15.6,6.6Hz,1H),6.00(d,J=6.9Hz,1H),7.20(d,J=5.5Hz,2H),8.57(d,J=5.5Hz,2H)

ＭＳ(SIMS)m/e：700$(M+H)^+$　$C_{43}H_{77}N_3O_4$(699)

実施例６２の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.08-1.45(m,22H),1.93-2.11(m,2H),2.00(s,3H),3.14(bs,1H),4.03-4.28(m,3H),4.34(dd,J=6.2,10.6Hz,1H),4.86(bs,2H),5.47(dd,J=6.2,15.4Hz,1H),5.74(dt,J=15.4,6.5Hz,1H),6.13(d,J=6.8Hz,1H)

ＭＳ(SIMS)m/e：385$(M+H)^+$　$C_{21}H_{40}N_2O_4$(384)

実施例６３の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.18(s,9H),1.20-1.44(m,22H),1.90-2.12(m,4H),2.88(d,J=4.9Hz,3H),2.90(s,6H),2.96-3.54(m,4H),4.12-4.40(m,3H),5.48(m,1H),5.78(dt,J=15.2,6.6Hz,1H),6.33(m,1H)

ＭＳ(SIMS)m/e：526$(M+H)^+$　$C_{30}H_{59}N_3O_4$(525)

実施例６４の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.79(t,J=6.3Hz,3H),1.00(d,J=6.8Hz,3H),1.03(d,J=6.8Hz,3H),1.00-1.40(m,22H),1.84-2.05(m,2H),2.04(s,3H),2.30(m,1H),3.98-4.35(m,4H),5.38(dd,J=6.3,15.4Hz,1H),5.66(dt,J=15.4,6.6Hz,1H),6.72(d,J=7.9Hz,1H),7.23(d,J=8.9Hz,2H),7.35(d,J=8.9Hz,2H)

ＭＳ(SIMS)m/e：546$(M+H)^+$　$C_{31}H_{51}N_3O_5$(545)

実施例６５

３-Ｏ-(tert-ブチルジメチルシリル)-２-Ｎ-イソブチリル-Ｄ-エリスロースフィンゴシン(30mg,0.062mmol)をテトラヒドロフラン(0.5ml)に溶かし、トリエチルアミン(１滴)及びメチルイソシアナート(90mg,0.92mmol)を加え、60℃で６時間撹拌した。反応混合物を減圧にて濃縮後、残留物をテトラヒドロフラン(0.5ml)に溶かし、フッ化テトラブチルアンモニウム(テトラヒドロフラン1M溶液，0.80ml)を加

え、室温で４時間攪拌した。残留物をカラムクロマトグラフィーで精製し、１－Ｏ－メチルアミノカルボニル－２－Ｎ－イソブチリル－Ｄ－エリスロ－スフィンゴシン(16mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm):0.83(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.45(m,22H),1.90-2.10(m,2H),2.36(m,1H),2.77(d,J=4.9Hz,3H),3.58(bs,1H),3.98-4.25(m,3H),4.38(dd,J=6.8,11.2Hz,1H),4.96(m,1H),5.44(dd,J=6.3,15.4Hz,1H),5.71(dt,J=6.4,15.4Hz,1H),6.21(d,J=7.1Hz,1H)

ＭＳ(CI)m/e：427$(M+H)^+$　$C_{24}H_{46}N_2O_4$(426)

実施例６６～７２

実施例６５の方法と同様にして実施例６５～７１の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

実施例６６の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,3H),1.13(d,J=6.8Hz,3H),1.13-1.46(m,22H),1.92-2.11(m,2H),2.37(m,1H),3.17(bs,1H),4.10-4.37(m,3H),4.47(dd,J=6.8,10.8Hz,1H),5.48(dd,J=6.3,15.4Hz,1H),5.75(dt,J=15.4,6.9Hz,1H),6.14(d,J=7.6Hz,1H),7.07(m,1H),7.13(bs,1H),7.23-7.44(m,4H)

ＭＳ(CI)m/e489$(M+H)^+$　$C_{29}H_{48}N_2O_4$(488)

実施例６７の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.3Hz,3H),1.11(d,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.42(m,22H),1.91-2.10(m,2H),2.38(m,1H),3.00(m,1H),4.16-4.57(m,4H),5.48(dd,J=6.3,15.4Hz,1H),5.78(dt,J=15.4,6.5Hz,1H),6.09(d,J=7.8Hz,1H),7.25-7.49(m,2H),7.49-7.65(m,2H),7.72(bs,1H)

ＭＳ(CI)m/e557$(M+H)^+$　$C_{30}H_{47}F_3N_2O_4$(556)

実施例６８の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.8Hz,3H),1.04-1.46(m,22H),1.92-2.12(m,2H),2.37(m,1H),3.21(bs,1H),3.78(s,3H),4.10-4.35(m,3H),4.46(dd,J=6.7,10.9Hz,1H),5.47(dd,J=6.3,15.4Hz,1H),5.74(dt,J=15.4,6.6Hz,1H),6.11(d,J=7.4Hz,1H),6.74-6.94(m,2H),7.14-7.38(m,2H)

ＭＳ(CI)m/e：519$(M+H)^+$　$C_{30}H_{50}N_2O_5$(518)

実施例６９の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.88(t,J=6.4Hz,3H),1.12(d,J=6.8Hz,3H),1.14(d,J=6.8Hz,3H),1.10-1.45(m,22H),1.92-2.12(m,2H),2.38(m,1H),3.00(bs,1H),3.87(s,3H),4.14-4.38(m,3H),4.49(m,1H),5.49(dd,J=6.3,15.4Hz,1H),5.76(dt,J=15.4,6.6Hz,1H),6.07(d,J=7.8Hz,1H),7.22(bs,1H),7.38(m,1H),7.62-7.81(m,2H),7.98(s,1H)

ＭＳ(SIMS)m/e：547$(M+H)^+$　$C_{31}H_{50}N_2O_6$(546)

実施例７０の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.87(t,J=6.4Hz,3H),1.06(t,J=6.8Hz,3H),1.09(t,J=6.8Hz,3H),1.11-1.48(m,22H),1.90-2.12(m,2H),2.32(m,1H),4.08-4.43(m,4H),5.42(dd,J=5.9,15.4Hz,1H),5.74(dt,J=15.4,6.7Hz,1H),6.14(d,J=7.7Hz,1H),7.47-7.71(m,3H),7.95-8.09(m,2H)

ＭＳ(SIMS)m/e：575$(M+Na)^+$　$C_{29}H_{48}N_2O_6S$(552)

実施例７１の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.88(t,J=6.9Hz,3H),1.21(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.55(d,J=7.0Hz,1H),4.24(m,2H),4.49(m,2H),5.53(dd,J=5.9,15.5Hz,1H),5.82(dt,J=15.6,6.7Hz,1H),6.58(d,J=7.4Hz,1H),7.51(m,2H),7.62(m,1H),7.85(m,1H),8.31(s,1H)

実施例７２の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.29(t,J=7.1Hz,3H),2.02(m,2H),3.20(bs,1H),3.39(d,J=5.1Hz,2H),4.05-4.25(m,3H),4.23(q,J=7.2Hz,2H),4.45(dd,J=6.2,11.1Hz,1H),5.31(m,1H),5.45(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.4,6.5Hz,1H),6.26(d,J=6.7Hz,1H)

実施例７３

４-(メチルチオ)アニリン(56mg,0.4mmol)のテトラヒドロフラン(１ml)溶液に、二炭酸ジ-tert-ブチル(109mg,0.50mmol)を加え、次いでＮ,Ｎ-ジメチルアミノピリジン(49mg,0.4mmol)を加えた後、室温で30分間攪拌した。この反応液に、３-Ｏ-(tert-ブチルジメチルシリル)-２-Ｎ-イソブチリル-Ｄ-エリスロ-スフィンゴシン(48

mg,0.10mmol)のテトラヒドロフラン(１ml)溶液を加え、室温で12時間攪拌した。この反応液を減圧下で濃縮し、残留物をカラムクロマトグラフィーで精製し、１-O-[４-(メチルチオ)アニリノカルボニル）]-２-N-イソブチリル-３-O-(tert-ブチルジメチルシリル)-D-エリスロ-スフィンゴシン(30mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.00(s,3H),0.03(s,3H),0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.11(d,J=6.9Hz,3H),1.12-1.55(m,22H),1.92-2.12(m,2H),2.31(m,1H),2.45(s,3H),4.10-4.30(m,3H),4.48(m,1H),5.41(dd,J=6.2,15.5Hz,1H),5.67(dt,J=15.5,6.7Hz,1H),5.85(d,J=8.1Hz,1H),6.95(s,1H),7.15-7.40(m,4H)

ここで得られた化合物(30mg,0.046mmol)をテトラヒドロフラン(1ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(1M溶液として0.5ml)を加え、同温度下５時間攪拌した。反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、１-O-[４-(メチルチオ)アニリノカルボニル]-２-N-イソブチリル-D-エリスロ-スフィンゴシン(14mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$-CD_3OD) δ (ppm)：0.81(t,J=6.3Hz,3H),1.02(d,J=6.7Hz,3H),1.05(d,J=6.9Hz,3H),0.90-1.40(m,22H),1.84-2.05(m,2H),2.32(m,1H),3.20(s,3H),3.95-4.38(m,4H),5.39(dd,J=6.2,15.3Hz,1H),5.68(dt,J=15.3,6.6Hz,1H),6.65(d,J=7.9Hz,1H),7.15(d,J=8.6Hz,2H),7.27(d,J=8.6Hz,2H)

ＭＳ(SIMS)m/e：535$(M+H)^+$　$C_{30}H_{50}N_2O_4S$(534)

実施例７５

３-O-(tert-ブチルジメチルシリル)-２-N-ピバロイル-D-エリスロ-スフィンゴシン(0.90mg,1.8mmol)をジメチルスルホキシド(12ml)とテトラヒドロフラン(12ml)の混合溶媒に溶かし、トリエチルアミン(6ml)を加えた後、氷冷した。この溶液に三酸化硫黄ピリジン錯体(2.84g,18mmol)を加え、30分間攪拌した。反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。抽出液を硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(1'Ｓ,2'Ｒ,3'Ｅ)-N-[２-(tert-ブチルジメチルシリルオキシ)-１-ホルミル-３-ヘプタデセニル]ピバルアミド（アルデヒド体）(0.80g)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.00(s,3H),0.01(s,3H),0.86(s,9H),0.89(t,3H),1.23(s,9H),1.23-1.38(m,22H),2.08(m,2H),4.48-4.57(m,2H),5.67(dd,J=6.0,15.4Hz,1H),5.89(dt,J=15.2,7.0Hz,1H),6.52(d,J=6.1Hz,1H),9.71(s,1H)

ここで得られたアルデヒド体(0.86g,1.8mmol)及び塩酸ヒドロキシルアミン(0.47g,6.7mmol)をテトラヒドロフラン(12ml)に溶かし、N,N-ジイソプロピルエチルアミン(1.16g,9.0mmol)を加え、室温で３時間攪拌した。反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(１'Ｓ,２'Ｒ,３'Ｅ)-Ｎ-[-(tert-ブチルジメチルシリルオキシ)-１-ヒドロキシイミノメチル-３-ヘプタデセニル]ピバルアミド（ヒドロキシルイミン体）(0.88g)を得た。

ここで得られたヒドロキシルイミン体(3.18g,6.2mmol)をテトラヒドロフラン(50ml)に溶かし、氷冷下、無水酢酸(0.70ml)、ピリジン(0.70ml,8.7mmol)を順次加え、20分間攪拌した。反応液に水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(１'Ｓ,２'Ｒ,３'Ｅ)-Ｎ-[１-アセトキシイミノメチル-２-(tert-ブチルジメチルシリルオキシ)-３-ヘプタデセニル]ピバルアミド（アセトキシイミン体）(2.53g)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.01(s,3H),0.04(s,3H),0.88(s,9H),0.88(t,3H),1.21(s,9H),1.21-1.40(m,22H),2.03(m,2H),2.16(s,3H),4.40(m,1H),4.66(m,1H),5.43(dd,J=6.7,15.5Hz,1H),5.74(dt,J=15.4,6.8Hz,1H),6.34(d,J=7.3Hz,1H),7.75(d,J=4.6Hz,1H)

ここで得られたアセトキシイミン体(2.53g,4.6mmol)のエタノール(200ml)溶液に、モリブデン酸(5.48g,37.5mmol)を加えた後、-30℃冷却下、水素化ホウ素ナトリウム(4.79g,127mmol)を加え、0℃まで昇温し、同温度にて48時間攪拌した。反応液に10％アンモニア水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(１'Ｓ,２'Ｒ,３'Ｅ)-Ｎ-[１-アミノメチル-２-(tert-ブチルジメチルシリルオキシ)-３-ヘプタデセニル]ピバルアミド（アミン体）(1.32g)を得た。

次に、４-ジメチルアミノピリジン(73mg,0.6mmol)のジクロロメタン(5ml)溶液に、二炭酸ジ-tert-ブチル(0.15mg,0.7mmol)を加え、次いで４-ピリジルメチルアミン(6

5mg,0.6mmol)を加えた後、室温で30分間攪拌した。この反応液に先の反応で得られたアミン体(99mg,0.2mmol)を加え、室温で５時間攪拌した。反応液を濃縮後、残留物をカラムクロマトグラフィーにより精製し、(1'S,2'R,3'E)-N-[2-(tert-ブチルジメチルシリルオキシ)-1-[[3-(4-ピリジルメチル)ウレイド]メチル]-3-ヘプタデセニル]ピバルアミド（ウレイド体）(94mg)を得た。

ここで得られたウレイド体(93mg,0.15mmol)をテトラヒドロフラン(1.8ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(１Ｍ溶液として1.8ml)を加え、同温度下20分間攪拌した。反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(1'S,2'R,3'E)-N-[2-ヒドロキシ-1-[[3-(4-ピリジルメチル)ウレイド]メチル]-3-ヘプタデセニル]ピバルアミド(94mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.12(s,9H),1.20-1.40(m,22H),2.02(m,2H),3.27(dt,J=4.9,14.4Hz,1H),3.50(m,1H),3.87(m,1H),4.10(m,1H),4.35(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.58(bs,1H),5.64(bs,1H),5.73(dt,J=15.4,6.6Hz,1H),6.65(d,J=6.4Hz,1H),7.19(d,J=4.6Hz),8.51(bs,1H)

ＭＳ(SIMS)m/e：517$(M+H)^+$　$C_{30}H_{52}N_4O_3$(516)

実施例７６～７８

実施例７５の方法と同様にして実施例７６～７８の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

実施例７６の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=7.1Hz,3H),1.19(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.25(m,1H),3.50(m,1H),3.72(bs,1H),3.91(m,1H),4.11(m,1H),4.59(bs,2H),5.28(bs,1H),5.47(dd,J=6.6,15.4Hz,1H),5.75(dt,J=15.4,6.8Hz,1H),6.61(bs,1H)

ＭＳ(SIMS)m/e：426$(M+H)^+$　$C_{24}H_{47}N_3O_3$(425)

実施例７７の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.76(d,J=4.9Hz,1H),3.25(dt,J=14.4,4.9Hz,1H),3.54(m,1H),3.90(m,1H),4.02(m,1H),4.09(m,1H),4.59(bs,1H),4.96(t,J=5.9Hz,1H),5.47(dd,J=6.5,15.4Hz,1H),5.74(dt,

J=15.4,6.6Hz,1H),6.71(d,J=6.5Hz,1H)

ＭＳ(SIMS)m/e：462$(M+Na)^+$　$C_{25}H_{49}N_3O_3$(439)

実施例７８の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.37(J=7.1Hz,3H),2.01(m,2H),3.36(dt,J=14.5,4.9Hz,1H),3.56(m,1H),3.94(m,1H),4.17(m,1H),4.34(m,2H),5.50(dd,J=6.4,15.5Hz,1H),5.77(dt,J=15.0,6.7Hz,1H),6.01(bs,1H),6.58(d,J=7.2Hz,1H),7.45(d,J=8.5Hz,1H),7.68(bs,1H),7.95(d,J=8.7Hz,1H)

ＭＳ(SIMS)m/e：596$(M+Na)^+$　$C_{33}H_{55}N_3O_5$(573)

実施例７９

(1'Ｓ,2'Ｒ,3'Ｅ)-Ｎ-[-１-アミノメチル-２-(tert-ブチルジメチルシリルオキシ)]-３-ヘプタデセニル]ピバルアミド（アミン体）(99mg,0.2mmol)のテトラヒドロフラン(4ml)溶液にピリジン(31mg,0.4mmol)を加え、-78℃冷却下クロロチオノギ酸フェニル(41μl,0.3mmol)を滴下後、１時間かけて-20℃まで加温した。反応液に飽和炭酸水素ナトリウム水を加え、酢酸エチルで抽出した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、(1'Ｓ,2'Ｒ,3'Ｅ)-Ｎ-[２-(tert-ブチルジメチルシリルオキシ)-１-(フェノキシチオカルボニルアミノメチル)-３-ヘプタデセニル]ピバルアミド(42mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.09(s,3H),0.88(t,J=7.1Hz,3H),0.94(s,9H),1.22(s,9H),1.20-1.43(m,22H),2.06(m,2H),3.78-3.92(m,2H),4.10(m,1H),4.34(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz,1H),6.32(d,J=7.7Hz,1H),7.04(d,J=7.9Hz,1H),7.25(d,J=7.9Hz,1H),7.38(d,J=7.9Hz,1H),7.89(m,1H)

ここで得られた化合物(86mg,0.14mmol)をジメチルスルホキシド(１ml)に溶かした後、４-ピリジルメチルアミン(15μl)を加え、室温で５時間攪拌した。反応液に水を加え、酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、(1'Ｓ,2'Ｒ,3'Ｅ)-Ｎ-[２-(tert-ブチルジメチルシリルオキシ)-１-[[３-(４-ピリジルメチル)チオウレイド]メチル]-３-ヘプタデセニル]ピバルアミド（チオウレイド体）(61mg)を得た。

ここで得られたチオウレイド体(60mg,0.10mmol)をテトラヒドロフラン(1.1ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(テトラヒドロフラン１Ｍ溶液，1.1ml)を加え、氷冷下６時間攪拌した。反応液に水を加え酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、(1'S,2'R,3'E)-N-[2-ヒドロキシ-1-[[3-(4-ピリジルメチル) チオウレイド]メチル]-3-ヘプタデセニル]ピバルアミド(35mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-1.43(m,22H),2.07(m,2H),3.65(m,1H),3.90(bs,1H),4.23(m,1H),4.76(bs,2H),5.50(dd,J=6.4,15.3Hz,1H),5.81(dt,J=15.2,6.9Hz,1H),6.44(bs,1H),7.26(m,2H),8.54(d,J=5.6Hz,2H)

ＭＳ(SIMS)m/e：533$(M+H)^+$　$C_{30}H_{52}N_4O_2S$(532)

実施例８０

3-O-(tert-ブチルジメチルシリル)-2-N-イソブチリル-D-エリスロ-スフィンゴシン(40mg,0.08mmol)をジクロロメタン(１ml)に溶かし、-78℃冷却下ピリジン(66mg,0.83mmol)を加え、次いでクロロぎ酸トリクロロメチル(26mg,0.13mmol)を加え、１時間かけて-20℃まで昇温した。この反応液に４-(tert-ブトキシカルボニルアミノ)アニリン(87mg,0.42mmol)を滴下し、１時間かけて室温に昇温した。反応液は室温で13時間攪拌した後、クロロホルムで抽出した。抽出液を１Ｍ塩酸、次いで飽和炭酸水素ナトリウム水で洗浄した後、水洗した。硫酸マグネシウムで乾燥後、濃縮し、残留物をカラムクロマトグラフィーで精製し、１-O-[[４－(tert-ブトキシカルボニルアミノ)フェニル]アミノカルボニル]-3-O-(tert-ブチルジメチルシリル)-2-N-イソブチリル-D-エリスロ-スフィンゴシン(25mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.00(s,3H),0.30(s,3H),0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.15-1.42(m,22H),1.50(s,9H),1.92-2.09(m,2H),2.30(m,1H),4.05-4.28(m,3H),4.48(m,1H),5.42(dd,J=6.2,15.4Hz,1H),5.67(dt,J=15.4,6.7Hz,1H),5.86(d,J=7.8Hz,1H),6.46(s,1H),6.81(s,1H),7.20-7.33(m,4H)

ここで得られた化合物(13mg,0.02mmol)を酢酸エチル(0.7ml)に溶かし、氷冷下４Ｍ塩化水素－酢酸エチル溶液(0.3ml)を加え、同温度下30分間攪拌した。反応液は

減圧で濃縮し、残留物を薄層クロマトグラフィーで精製し、1-O-[(4-アミノフェニル)アミノカルボニル]-2-N-イソブチリル-D-エリスロ-スフィンゴシン(8mg)を得た。

^{1}H－NMR($CDCl_3$-CD_3CD) δ (ppm)：0.79(t,J=6.4Hz,3H),1.01(d,J=6.8Hz,3H),1.02(d,J=6.9Hz,3H),1.00-1.40(m,22H),1.82-2.10(m,2H),2.30(m,1H),3.92-4.30(m,4H),5.37(dd,J=6.3,15.4Hz,1H),5.65(dt,J=15.4,6.2Hz,1H),6.58(d,J=8.4Hz,2H),6.74(bs,1H),7.07(d,J=8.4Hz,2H),8.20(s,1H)

MS(SIMS)m/e：504$(M+H)^+$ $C_{29}H_{49}N_3O_4$(503)

実施例81

1-O-[[3-(ジメチルアミノ)プロピル]アミノカルボニル]-2-N-ピバロイル-D-エリスロ-スフィンゴシン(40mg)のクロロホルム(1ml)溶液に、炭酸水素カリウム(0.5g)を加え、次いでヨウ化メチル(0.5ml)を加え、室温で16時間攪拌した。析出物をろ過した後、濃縮し1-O-[[3-(トリメチルアンモニオ)プロピル]アミノカルボニル]-2-N-ピバロイル-D-エリスロ-スフィンゴシン　ヨウ素塩(28mg)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.6Hz,3H),1.20(s,9H),1.20-1.44(m,22H),2.02(m,2H),2.13(m,2H),3.38(s,9H),3.38(m,1H),3.56(bs,1H),3.84(m,2H),4.17(m,2H),4.26(m,1H),4.31(dd,J=5.6,11.1Hz,1H),5.48(dd,J=6.8,15.4Hz,1H),5.80(dt,J=15.2,6.8Hz,1H),6.25(m,1H),6.36(d,J=8.5Hz,1H)

MS(SIMS)m/e：526$(M-127)^+$ $C_{30}H_{60}IN_3O_4$(654)

実施例82

3-O-(tert-ブチルジメチルシリル)-2-N-ピバロイル-D-エリスロ-スフィンゴシン(0.20g,0.4mmol)をジクロロメタン(8ml)に溶かし、-78℃に冷却した。この溶液に、ピリジン(320μl,4.0mmol)を加え、次いでクロロぎ酸トリクロロメチル(58μl,0.48mmol)を加え、1時間かけて-20℃まで昇温した。2-アミノエタノール(340μl,4.0mmol)のジクロロメタン(5ml)溶液を加えた後、4時間かけて室温まで昇温した。反応液は1M塩酸、飽和炭酸水素ナトリウム水、水、飽和食塩水で順次洗浄した。硫酸マグネシウムで乾燥後、溶媒を留去し、残留物をカラムクロマト

グラフィーで精製し、3-O-(tert-ブチルジメチルシリル)-1-O-[(2-ヒドロキシエチル)アミノカルボニル]-2-N-ピバロイル-D-エリスロ-スフィンゴシン(0.22g)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.00(s,3H),0.04(s,3H),0.87(t,J=6.7Hz,3H),0.90(s,9H),1.17(s,9H),1.12-1.47(m,22H),1.92-2.11(m,2H),3.08-3.50(m,3H),3.65(m,1H),3.78(m,1H),4.10-4.35(m,4H),5.24(t,J=5.4Hz,1H),5.39(dd,J=6.5,15.4Hz,1H),5.66(dt,J=15.4,6.6Hz,1H),6.12(m,1H)

ここで得られた化合物(80mg,0.14mmol)をジクロロメタン(3ml)に溶かした後、4-(ジメチルアミノ)ピリジン(17mg,0.14mmol)を加え、-78℃に冷却した。この反応液にピリジン(0.1ml)を加え、次いでクロロぎ酸トリクロロメチル(20μl,0.17mmol)を加えた。反応液は1時間かけて-20℃まで昇温した。反応液に25%アンモニア水(1.4ml)を加え、2時間かけて室温まで戻した。反応液を1M塩酸、飽和炭酸水素ナトリウム水、水、飽和食塩水で順次洗浄した。硫酸マグネシウムで乾燥後、溶媒を留去し、残留物をカラムクロマトグラフィーで精製し、3-O-(tert-ブチルジメチルシリル)-1-O-[[2-(カルバモイルオキシ)エチル]アミノカルボニル]-2-N-ピバロイル-D-エリスロ-スフィンゴシン(80mg)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：-0.02(s,3H),0.01(s,3H),0.86(t,J=6.8Hz,3H),0.87(s,9H),1.14(s,9H),1.12-1.44(m,22H),1.90-2.08(m,2H),3.28-3.52(m,2H),4.00-4.26(m,5H),4.39(m,1H),4.98(bs,2H),5.30(t,J=5.6Hz,1H),5.38(dd,J=5.6,15.4Hz,1H),5.64(dt,J=15.4,6.6Hz,1H),6.09(d,J=7.8Hz,1H)

ここで得られた化合物(50mg,0.08mmol)をテトラヒドロフラン(1ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(テトラヒドロフラン1M溶液、1.1ml)を加え、同温度下2.5時間攪拌した。反応液に水を加え、酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、1-O-[[2-(カルバモイルオキシ)エチル]アミノカルボニル]-2-N-ピバロイル-D-エリスロ-スフィンゴシン(25mg)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.10-1.42(m,22H),1.16(s,9H),1.90-2.10(m,2H),3.33-3.48(m,2H),3.75(m,1H),4.00-4.28(m,5H),4.39(dd,J=6.9,11.1Hz,1

H),5.01(bs,2H),5.43(dd,J=6.4,15.4Hz,1H),5.72(dt,J=15.4,6.5Hz,1H),6.33(d,J=7.3Hz,1H)

ＭＳ(SIMS)m/e：514$(M+H)^+$　$C_{27}H_{51}N_3O_6$(513)

実施例８３，８４

実施例８２の方法と同様にして実施例８３及び８４の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

実施例８３の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.82(m,2H),2.02(m,2H),3.26(m,2H),3.55(d,J=5.3Hz,1H),4.03-4.22(m,5H),4.41(dd,J=7.5,11.8Hz,1H),4.75(bs,2H),5.23(m,1H),5.47(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.3,6.6Hz,1H),6.34(d,J=7.4Hz,1H)

ＭＳ(SIMS)m/e：528$(M+H)^+$　$C_{28}H_{53}N_3O_6$ (527)

実施例８４の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm):0.87(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.18-1.45(m,22H),1.72-1.90(m,2H),1.95-2.10(m,2H),2.37(m,1H),2.90(s,6H),3.17-3.33(m,2H),3.54(d,J=5.1Hz,1H),4.00-4.16(m,3H),4.16(t,J=5.9Hz,2H),4.42(dd,J=6.4,11.4Hz,1H),5.27(t,J=6.1Hz,1H),5.43(dd,J=6.4,15.4Hz,1H),5.72(dt,J=15.4,6.6Hz,1H),6.41(d,J=7.4Hz,1H)

ＭＳ(SIMS)m/e：542$(M+H)^+$　$C_{29}H_{55}N_3O_6$(541)

実施例８５

３-Ｏ-(tert-ブチルジメチルシリル)-２-Ｎ-ピバロイル-Ｄ-エリスロ-スフィンゴシン(0.23mg,0.45mmol)をテトラヒドロフラン(７ml)に溶かし、４-(ジメチルアミノ)ピリジン(20mg,0.16mmol)及びイソシアノ酢酸エチル(0.11mg,0.9mmol)を加え、60℃にて20時間攪拌した。反応液を濃縮した後、残留物をテトラヒドロフラン(３ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(テトラヒドロフラン１Ｍ溶液、３ml)を加え、同温度下１時間攪拌した。反応液に水を加え酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、１-Ｏ-(エトキシカルボニルメチルアミノカルボニル)-２-Ｎ-ピバロイル-Ｄ-エリスロ-スフィンゴシン(0.20g)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.7Hz,3H),1.18(s,9H),1,20-1.40(m,22H),1.29(t,J=7.1Hz,3H),2.02(m,2H),3.39(d,J=5.1Hz,1H),3.42(d,J=5.5Hz,2H),4.05-4.25(m,3H),4.23(q,J=7.2Hz,2H),4.45(dd,J=6.2,11.1Hz,1H),5.31(m,1H),5.45(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.4,6.5Hz,1H),6.26(d,J=6.7Hz,1H)

MS(SIMS)m/e：513$(M+H)^+$ $C_{28}H_{52}N_2O_6$(512)

ここで得られた化合物(0.20g,0.39mmol)をテトラヒドロフラン(3ml)に溶かした後、2M水酸化ナトリウム水(2.8ml)を加え、室温で1時間攪拌した。反応液を2M塩酸で酸性にした後、酢酸エチルで抽出した。硫酸マグネシウムで乾燥した後、濃縮し、残留物をカラムクロマトグラフィーで精製し、1-O-(カルボキシルメチルアミノカルボニル)-2-N-ピバロイル-D-エリスロ-スフィンゴシン(0.18g)を得た。

^{1}H－NMR($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),3.80-4.10(m,2H),4.10-4.60(m,4H),5.45(dd,J=6.3,15.4Hz,1H),5.76(dt,J=15.4,6.6Hz,1H),5.76(m,1H),6.31(d,J=7.5Hz,1H)

MS(SIMS)m/e：507$(M+Na)^+$ $C_{26}H_{48}N_2O_6$(484)

実施例86～93

実施例85の方法と同様にして実施例86～93の化合物を製造した。各化合物の^{1}H－NMRスペクトル、マススペクトル等の物理化学データーを示す。

実施例86の化合物

^{1}H－NMR($CDCl_3$) δ (ppm)：0.87(t,J=6.3Hz,3H),1.16(s,9H),1.18-1.42(m,22H),1.42-1.76(m,4H),1.93-2.10(m,2H),2.35(t,J=6.7Hz,2H),3.05-3.24(m,2H),3.98-4.27(m,3H),4.38(dd,J=7.2,11.1Hz,1H),5.34(t,J=5.6Hz,1H),5.42(dd,J=6.2,15.4Hz,1H),5.72(dt,J=15.4,6.5Hz,1H),6.43(d,J=7.2Hz,1H)

MS(SIMS)m/e：527$(M+H)^+$ $C_{29}H_{54}N_2O_6$(526)

実施例87の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ (ppm)：0.83(t,J=6.2Hz,3H),1.05(d,J=6.5Hz,3H),1.08(d,J=6.5Hz,3H),1.08-1.50(m,22H),1.90-2.08(m,2H),2.34(m,1H),4.07-4.40(m,4H),5.43(dd,J=6.3,15.4Hz,1H),5.72(dt,J=15.4,6.5Hz,1H),6.53(d,J=7.9Hz,1H),7.43(d,J=8.7H

z,2H),7.94(d,J=8.7Hz,2H)

MS(SIMS)m/e：533$(M+H)^+$ $C_{30}H_{48}N_2O_6$(532)

実施例88の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.88(t,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.12(d,J=6.9Hz,3H),1.18-1.41(m,22H),1.95-2.05(m,2H),2.39(m,1H),4.15(m,1H),4.18-4.27(m,2H),4.36(m,1H),5.48(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz,1H),7.37(dd,J=7.5,7.7Hz,1H),7.73(d,J=7.7Hz,2H),7.97(s,1H)

MS(SIMS)m/e：533 $(M+H)^+$ $C_{30}H_{49}N_2O_6$(532)

実施例89の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.87(t,J=6.4Hz,3H),1.08-1.50(m,22H),1.14(d,J=6.8Hz,6H),1.88-2.14(m,2H),2.44(m,1H),4.13-4.58(m,4H),5.50(dd,J=6.4,15.4Hz,1H),5.78(dt,J=15.4,6.4Hz,1H),6.41(d,J=7.4Hz,1H),7.02(m,1H),7.51(m,1H),8.05(d,J=8.0Hz,1H),8.34(d,J=8.3Hz,1H),10.72(s,1H)

MS(CI)m/e：533 $(M+H)^+$ $C_{30}H_{48}N_2O_6$(532)

実施例90の化合物

^{1}H－NMR($CDCl_3$-CD_3OD) δ(ppm)：0.84(t,J=6.3Hz,3H),1.06(d,J=6.3Hz,3H),1.07(d,J=6.3Hz,3H),1.05-1.43(m,22H),1.88-2.07(m,2H),2.32(m,1H),3.95-4.42(m,6H),5.41(dd,J=6.1,15.4Hz,1H),5.70(dt,J=15.4,6.4Hz,1H),6.21(bs,1H),6.44(d,J=7.0Hz,1H),7.29(d,J=8.2Hz,2H),7.95(d,J=8.2Hz,2H)

MS(SIMS)m/e：547 $(M+H)^+$ $C_{31}H_{50}N_2O_6$(546)

実施例91の化合物

^{1}H－NMR(500MHz, $CDCl_3$-CD_3OD) δ(ppm)：0.88(t,J=6.9Hz,3H),1.10(d,J=6.8Hz,3H),1.12(d,J=6.7Hz,3H),1.19-1.40(m,16H),1.95-2.08(m,2H),2.36(m,1H),4.07-4.22(m,2H),4.27-4.45(m,4H),5.45(dd,J=6.5,15.3Hz,1H),5.74(dt,J=15.3,6.8Hz,1H),7.34(d,J=8.0Hz,2H),8.00(d,J=8.0Hz,2H)

MS(SIMS)m/e：505 $(M+H)^+$ $C_{28}H_{44}N_2O_6$(504)

実施例92の化合物

^{1}H－NMR($CDCl_3$) δ(ppm)：0.87(t,J=6.6Hz,3H),1.22(s,9H),1.20-1.40(m,22H),2.

06(m,2H),3.42-3.66(m,2H),4.03(m,1H),4.27(m,1H),5.53(dd,J=6.5,15.4Hz,1H),5.83(dt,J=15.4,6.6Hz,1H),6.43(bs,1H),6.57(d,J=7.1Hz,1H),7.63(d,J=8.5Hz,1H),8.04(d,J=8.6Hz,1H),8.55(bs,1H),12.0(bs,1H)

ＭＳ(SIMS)m/e：546$(M+H)^+$　$C_{31}H_{51}N_3O_5$(545)

実施例９３の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.86(t,J=6.7Hz,3H),1.07(s,9H),1.20-1.40(m,22H),1.96(m,2H),2.05-2.12(m,2H),3.73(m,1H),3.93(m,1H),5.02(bs,1H),5.39(dd,J=6.5,15.4Hz,1H),5.59(dt,J=15.3,6.7Hz,1H),5.65(bs,2H),5.88(t,J=5.7Hz,1H),6.95(d,J=8.5Hz,1H),7.21(s,2H),8.24(d,J=8.0Hz,1H),8.39(s,1H)

ＭＳ(SIMS)m/e：560$(M+H)^+$　$C_{31}H_{53}N_5O_4$(559)

実施例９４

２-Ｎ-(tert-ブトキシカルボニル)-１-Ｏ-ピバロイル-Ｄ-エリスロ-スフィンゴシン(参考例5の化合物)(1.2g,2.5mmol)をＮ,Ｎ-ジメチルホルムアミド(13ml)に溶かし、イミダゾール(1.4g,20mmol)を加え、次いでtert-ブチルジメチルシリルクロリド(0.88g,5.8mmol)を加え、室温にて３時間攪拌した。反応液を減圧にて濃縮した後、残留物をカラムクロマトグラフィーで精製し、２-Ｎ-(tert-ブトキシカルボニル)-３-Ｏ-(tert-ブチルジメチルシリル)-１-Ｏ-ピバロイル-Ｄ-エリスロ-スフィンゴシン(1.5g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.00(s,3H),0.03(s,3H),0.87(t,J=6.6Hz,3H),0.88(s,9H),1.07-1.45(m,22H),1.19(s,9H),1.42(s,9H),1.93-2.09(m,2H),3.85(m,1H),4.04-4.30(m,3H),4.64(d,J=9.3Hz,1H),5.39(dd,J=6.6,15.5Hz,1H),5.65(dt,J=15.5,6.5Hz,1H)

ここで得られた化合物(1.3g,2.2mmol)を脱水メタノール(16ml)に溶かし、１,８-ジアザビシクロ[５.４.０]ウンデセ-７-エン(0.50g,3.3mmol)を加え、室温で24時間攪拌した。反応液を減圧にて濃縮し、残留物をカラムクロマトグラフィーで精製し、２-Ｎ-(tert-ブトキシカルボニル)-３-Ｏ-(tert-ブチルジメチルシリル)-Ｄ-エリスロ-スフィンゴシン(1.1g)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.02(s,3H),0.07(s,3H),0.87(t,J=6.8Hz,3H),0.89(s,9H),1.10-1.48(m,22H),1.45(s,9H),1.94-2.10(m,2H),3.00(d,J=9.6Hz,1H),3.44(m,1H),3.5

6(m,1H),4.03(m,1H),4.47(m,1H),5.34(d,J=7.7Hz,1H),5.44(dd,J=6.1,15.5Hz,1H),5.71(dt,J=15.5,6.6Hz,1H)

ここで得られた化合物(0.15g,0.29mmol)をジクロロメタン(６ml)に溶かした後、４-(ジメチルアミノ)ピリジン(35mg,0.29mmol)を加え、-78℃冷却下クロロぎ酸トリクロロメチル(86mg,0.44mmol)を加えた後、１時間かけて-20℃まで昇温した。この反応液に、25％アンモニア水(１ml)を滴下し、３時間かけて室温まで昇温した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥した後、溶媒を留去した。残留物をカラムクロマトグラフィーで精製し、２-N-(tert-ブトキシカルボニル)-３-O-(tert-ブチルジメチルシリル)-１-O-カルバモイル-D-エリスロ-スフィンゴシン(0.15g)を得た。

^{1}Ｈ－ＮＭＲ(CDCl$_3$) δ (ppm)：-0.01(s,3H),0.03(s,3H),0.82-0.93(m,9H),0.87(s,9H),1.13-1.52(m,22H),1.43(s,9H),1.92-2.09(m,2H),3.77(bs,1H),4.05-4.30(m,3H),4.62-4.85(bs,3H),5.38(dd,J=6.6,15.4Hz,1H),5.65(dt,J=15.4,6.6Hz,1H)

ここで得られた化合物(0.13g,0.24mmol)をテトラヒドロフラン(1.2ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(テトラヒドロフラン１Ｍ溶液、2.0ml)を加え、同温度下６時間攪拌した。反応液に水を加え酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、２-N-(tert-ブトキシカルボニル)-１-O-カルバモイル-D-エリスロ-スフィンゴシン(0.15g)を得た。

^{1}Ｈ－ＮＭＲ(CDCl$_3$) δ (ppm)：0.88(t,J=6.4Hz,3H),1.05-1.42(m,22H),1.44(s,9H),1.95-2.11(m,2H),2.73(bs,1H),3.86(bs,1H),4.04-4.18(m,2H),4.34(dd,J=6.0,11.5Hz,1H),4.67(bs,2H),4.89(bs,1H),5.48(dd,J=6.6,15.0Hz,1H),5.74(dt,J=15.0,6.0Hz,1H)

ＭＳ(SIMS)m/e：443$(M+H)^+$　　$C_{24}H_{46}N_2O_5$(442)

実施例９５

実施例９４の方法と同様にして実施例９５の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

^{1}Ｈ－ＮＭＲ(CDCl$_3$) δ (ppm)：0.86(t,J=6.4Hz,3H),1.11-1.48(m,22H),1.41(s,9H),1.92-2.10(m,2H),3.17(bs,1H),3.87(m,1H),4.05-4.42(m,5H),5.00(d,J=8.3Hz,1H),5.47(dd,

J=6.4,15.4Hz,1H),5.66(bs,1H),5.72(dt,J=15.4,6.3Hz,1H),7.19(d,J=5.9Hz,2H),8.52(d,J=5.9Hz,2H)

ＭＳ(SIMS)m/e：534 $(M+H)^+$ $C_{30}H_{51}N_3O_5$(533)

実施例９６

２-Ｎ-(tert-ブトキシカルボニル)-１-Ｏ-カルバモイル-Ｄ-エリスロ-スフィンゴシン(20mg)に、氷冷下トリフルオロ酢酸(0.5ml)を加え、同温度下30分間撹拌した。反応液を減圧にて濃縮し、残留物にエタノールを加え、再び濃縮した。残留物に4M塩化水素-酢酸エチル溶液(0.5ml)を加え、減圧下で濃縮し、1-Ｏ-カルバモイル-Ｄ-エリスロ-スフィンゴシン塩酸塩(12mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.84(t,J=6.4Hz,3H),1.08-1.43(m,22H),1.93-2.11(m,2H),3.37(m,1H),4.10(dd,J=8.9,12.0Hz,1H),4.29(dd,J=3.4,12.0Hz,1H),4.41(m,1H),5.39(dd,J=6.2,15.2Hz,1H),5.83(dt,J=15.2,6.8Hz,1H)

ＭＳ(SIMS)m/e：343$(M+H)^+$ $C_{19}H_{38}N_2O_3$(342)

実施例９７，９８

実施例９６の方法と同様にして実施例９７及び９８の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

実施例９７の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$-CD_3OD) δ (ppm)：0.79(t,J=6.2Hz,3H),1.00-1.42(m,22H),1.88-2.06(m,2H),3.37(m,1H),4.13(m,1H),4.22-4.40(m,2H),4.50(bs,2H),5.35(dd,J=6.4,15.3Hz,1H),5.79(dt,J=15.3,6.8Hz,1H),7.89(d,J=5.4Hz,2H),8.64(d,J=5.4Hz,2H)

ＭＳ(SIMS)m/e：434$(M+H)^+$ $C_{25}H_{43}N_3O_3$(433)

実施例９８の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.03-1.42(m,22H),1.88-2.07(m,2H),3.53(m,1H),4.20-4.60(m,3H),5.41(dd,J=6.6,15.4Hz,1H),5.28(dt,J=15.4,6.8Hz,1H),6.98(m,1H),7.21(m,1H),7.30(d,J=8.0Hz,1H),7.59(s,1H),7.97(d,J=7.2Hz,1H)

ＭＳ(CI)m/e：453$(M+H)^+$ $C_{25}H_{41}ClN_2O_3$(452)

実施例９９

２-Ｎ-(tert-ブトキシカルボニル)-３-Ｏ-(tert-ブチルジメチルシリル)-１-[(４

-ピリジル)メチルアミノカルボニル]-D-エリスロ-スフィンゴシン(46mg)に、氷冷下トリフルオロ酢酸(１ml)を加え、同温度下30分間撹拌した。反応混合物は減圧下濃縮し、残留物にエタノールを加え、再び減圧下濃縮した。残留物をテトラヒドロフランに溶かし、１-ヒドロキシベンゾトリアゾール１水和物(15mg)とN-(tert-ブトキシカルボニル)グリシン(19mg)を加え、氷冷下トリエチルアミン(35mg)及び１-エチル-３-(３-ジメチルアミノプロピル)カルボジイミド塩酸塩(21mg)のクロロホルム(１ml)溶液を加え、室温に昇温しながら３時間撹拌した。反応液に１M塩酸を加え、クロロホルムで抽出した。抽出液を飽和炭酸水素ナトリウム水、水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、２-N-[N-(tert-ブトキシカルボニル)グリシル]-３-O-(tert-ブチルジメチルシリル)-１-O-[(４-ピリジル)メチルアミノカルボニル]-D-エリスロ-スフィンゴシン(25mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：-0.01(s,3H),0.02(s,3H),0.86(t,J=6.8Hz,3H),0.88(s,9H),1.10-1.50(m,22H),1.42(s,9H),1.88-2.02(m,2H),3.67(dd,J=5.5,16.8Hz,1H),3.82(dd,J=6.3,16.8Hz,1H),4.06-4.28(m,4H),4.34(d,J=6.2Hz,2H),5.09(bt,1H),5.38(dd,J=6.1,15.3Hz,1H),5.50-5.75(m,2H),6.35(d,J=7.2Hz,1H),7.19(d,J=5.9Hz,2H),8.53(d,J=5.9Hz,2H)

ここで得られた化合物(22mg)をテトラヒドロフラン(0.5ml)に溶かし、氷冷下フッ化テトラブチルアンモニウム(テトラヒドロフラン１M溶液、0.5ml)を加えた後、同温度下４時間、次いで室温で２時間撹拌した。反応液に水を加え酢酸エチルで抽出した。水洗後、硫酸マグネシウムで乾燥し、溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、２-N-[N-(tert-ブトキシカルボニル)グリシル]-１-O-[(４-ピリジル)メチルアミノカルボニル]-D-エリスロ-スフィンゴシン(17mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.87(t,J=6.4Hz,3H),1.10-1.48(m,22H),1.42(s,9H),1.91-2.10(m,2H),3.28(bs,1H),3.63-3.86(m,2H),4.04-4.40(m,6H),5.30(bt,1H),5.45(dd,J=5.7,15.4Hz,1H),5.74(dt,J=15.4,5.7Hz,1H),5.87(t,J=6.1Hz,1H),6.78(d,J=6.8Hz,1H),7.13-7.23(m,2H),8.49-8.59(m,2H)

ＭＳ(SIMS)m/e：591$(M+H)^+$　$C_{32}H_{54}N_4O_6$(590)

実施例１００

氷冷下、2-N-[N-(tert-ブトキシカルボニル)グリシル]-１-[(４-ピリジル)メチルアミノカルボニル]-D-エリスロ-スフィンゴシン(12mg)にトリフルオロ酢酸(0.5ml)を加え、同温度下30分間撹拌した。反応液を減圧にて濃縮し、残留物にエタノールを加え、再び濃縮した。残留物に４M塩化水素－酢酸エチル溶液を加え、減圧下濃縮した後、残留物を薄層クロマトグラフィーで精製し、2-N-グリシル-１-O-[(４-ピリジル)メチルアミノカルボニル]-D-エリスロ-スフィンゴシン(８mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.88(t,J=6.9Hz,3H),1.19-1.41(m,22H),1.98-2.07(m,2H),3.69-3.83(m,2H),3.93(m,1H),4.16-4.28(m,2H),4.43(m,1H),4.46(d,J=17.9Hz,1H),4.65(d,J=17.9Hz,1H),5.47(dd,J=6.4,15.3Hz,1H),5.77(dt,J=15.3,6.7Hz,1H),8.05(d,J=6.0Hz,2H),8.74(d,J=6.0Hz,2H)

ＭＳ(SIMS)m/e：491$(M+H)^+$　$C_{27}H_{46}N_4O_4$(490)

実施例１０１，１０２

実施例１００の方法と同様にして実施例１０１及び１０２の化合物を製造した。各化合物の^{1}Ｈ－ＮＭＲスペクトル、マススペクトル等の物理化学データーを示す。

実施例１０１の化合物

^{1}Ｈ－ＮＭＲ($CDCl_3$) δ (ppm)：0.85(t,J=6.4Hz,3H),1.12-1.47(m,22H),1.39(s,3H),1.42(s,9H),1.47(s,3H),1.89-2.08(m,2H),3.91(bs,1H),4.05-4.38(m,6H),5.08(s,1H),5.42(dd,J=6.1,15.4Hz,1H),5.72(dt,J=15.4,6.1Hz,1H),5.93(t,J=6.0Hz,1H),6.83(d,J=7.7Hz,1H),7.19(d,J=5.9Hz,2H),8.50(d,J=5.9Hz,2H)

ＭＳ(SIMS)m/e：619$(M+H)^+$　$C_{34}H_{58}N_4O_6$(618)

実施例１０２の化合物

^{1}Ｈ－ＮＭＲ(DMSO-d_6) δ (ppm):0.85(t,J=6.3Hz,3H),1.10-1.40(m,22H),1.43(s,3H),1.48(s,3H),1.85-2.02(m,2H),3.85-4.10(m,3H),4.28-4.50(m,3H),5.36(dd,J=4.2,15.0Hz,1H),5.89(dt,J=15.0,6.3Hz,1H),7.85(d,J=6.1Hz,2H),7.92(d,J=5.7Hz,1H),8.12(d,J=7.1H

z,1H),8.27(bs,3H),8.82(d,J=5.7Hz,2H)

ＭＳ(SIMS)m/e：519$(M+H)^+$　$C_{29}H_{50}N_4O_4$(518)

実施例１０３

２-Ｎ-(tert-ブトキシカルボニル)-１-Ｏ-[(４-ピリジル)メチルアミノカルボニル]-Ｄ-エリスロ-スフィンゴシン(65mg,0.11mmol)を氷冷し、トリフルオロ酢酸(1ml)を加え、同温度下１時間攪拌した。反応液を減圧下濃縮し、残留物にエタノールを加え、再び濃縮した。残留物をテトラヒドロフラン(１ml)に溶かし、氷冷下トリエチルアミン(23mg,0.23mmol)を加え、次いで塩化グリオキシル酸エチル(14mg,0.1mmol)を滴下し、同温度下２時間攪拌した。反応液に酢酸エチルを加え抽出し、有機層を水、飽和食塩水で順次洗浄した後、無水硫酸ナトリウムで乾燥した。溶媒を留去した後、残留物をカラムクロマトグラフィーで精製し、(１'Ｓ,２'Ｒ,ｒ３'Ｅ)-Ｎ-[２-ヒドロキシ-１-[(４-ピリジル)メチルアミノカルボニルオキシメチル]-３-ヘプタデセニル]オキサミド酸　エチルエステル(23mg)を得た。

^{1}Ｈ－ＮＭＲ($CDCl_3$)δ(ppm)：0.87(t,J=6.2Hz,3H),1.10-1.42(m,22H),1.36(t,J=7.1Hz,3H),1.90-2.10(m,2H),3.00(bs,1H),4.12-4.48(m,8H),5.40-5.58(m,2H),5.76(dt,J=15.2,6.5Hz,1H),7.19(d,J=5.6Hz,2H),7.53(d,J=7.6Hz,1H),8.52(d,J=5.6Hz,2H)

ＭＳ(SIMS)m/e：534$(M+H)^+$　$C_{29}H_{47}N_3O_6$(533)

実施例１０４

(１'Ｓ,２'Ｒ,３'Ｅ)-Ｎ-[２-ヒドロキシ-１-[(４-ピリジル)メチルアミノカルボニルオキシメチル]-３-ヘプタデセニル]オキサミド酸　エチルエステル(実施例１０３の化合物)(18mg,0.034mmol)をメタノール(1.5ml)とテトラヒドロフラン(１ml)の混合溶媒に溶かし、２Ｍ水酸化ナトリウム水を加え、室温で45分間攪拌した。反応液に１Ｍ塩酸を加え、pH4.0に調整した後、減圧下濃縮した。残留物をクロロホルム-メタノールの混合溶媒で抽出した後、不溶物をろ過して除いたろ液を減圧下濃縮し、(１'Ｓ,２'Ｒ,３'Ｅ)-Ｎ-[２-ヒドロキシ-１-[(４-ピリジル)メチルアミノカルボニルオキシメチル]-３-ヘプタデセニル]オキサミド酸(10mg)を得た。

^{1}Ｈ－ＮＭＲ(DMSO-d_6)δ(ppm)：0.85(t,J=6.9Hz,3H),1.05-1.46(m,22H),1.85-2.02(m,2H),3.86-4.11(m,3H),4.26-4.45(m,3H),5.30(bt,1H),5.35(dd,J=6.3,15.4Hz,1H),5.56

(dt,J=15.4,6.8Hz,1H),7.69(bs,2H),7.92(d,J=5.9Hz,1H),8.54(d,J=8.8Hz,1H),8.73(bs,2H),13.40(bs,1H)

ＭＳ(SIMS)m/e：507$(M+H)^+$　$C_{27}H_{43}N_3O_6$(505)

試験例　［中性スフィンゴミエリナーゼ阻害試験］

（酵素調製）

スフィンゴミエリナーゼの酵素源としてラット大脳を用い、ミクロソーム画分を以下の様に調製した。10匹のウイスター雄性ラット(４週齢)を断頭後、全脳を摘出した。更に小脳を除去し、予め４℃に冷却したバッファーA(10%ショ糖、20mM Hepes-KOH(pH7.4)、20unit/mlアプロチニン、0.1mM PMSF、10μg/mlロイペプチン)120mlを加え、４℃冷却下、ホモジナイザーを用いて、脳細胞を破砕した。次に細胞破砕液を４℃冷却下、600×g、10分間の遠心分離を行い、その上清を更に12,000×gで15分間の遠心分離を行った。最後に得られた上清を100,000×gで60分間の超遠心分離を行い、その沈殿物をミクロソーム画分とした。この画分を更に、バッファーB(10%ショ糖、20mM Hepes-KOH(pH7.4)、40unit/mlアプロチニン、0.2mM PMSF、20μg/mlロイペプチン)５mlに再懸濁し、－80℃で凍結保存し、使用時にバッファーC(20mM Hepes-KOH(pH7.4)-２mM $MgCl_2$)で蛋白質濃度２mg/mlになるように調整した。

（基質溶液の調製）

26.5mgのスフィンゴミエリン(牛、脳；シグマ社製)を10w/v%トリトンX 375μlで溶解後、バッファーC14.6mlを添加してスフィンゴミエリン溶液とした。新たに、400μlのN-メチル-^{14}C-スフィンゴミエリン(牛、48mCi/mmol,25μCi/ml；アマシャム社製)の溶媒を乾固し、残査をエタノール50μlに再度溶解し、前述の12mlのスフィンゴミエリン溶液を加え、基質溶液とした。

（試験方法）

スフィンゴミエリナーゼ反応は、検体のジメチルスルホキシド溶液10μl、バッファーD(20mM Hepes-KOH(pH7.4)-２mM $MgCl_2$、0.08w/v%トリトンX)70μl、酵素溶液10μl、基質溶液 10μlを混合後、37℃、３時間インキュベーションするこ

とにより行った。反応終了後、クロロホルム：メタノール(2:1、v/v)を500μl加えて抽出操作を施し、得られた水層より150μlを2mlのアクアゾール2と混和して、反応生成物である^{14}C-ホスホリルコリンを測定した。スフィンゴミエリナーゼ活性は酵素無添加の場合の測定値を差し引いた値として計算した。

その結果を表2に示した。

表2

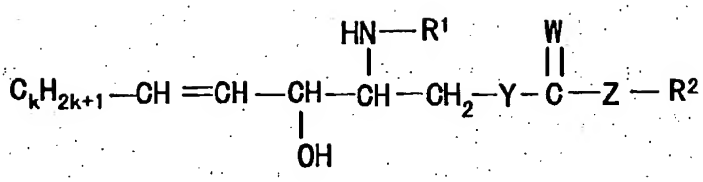
実施例	IC_{50}（μM）	実施例	IC_{50}（μM）
1	3.7	38	5.5
3	4.9	42	6.7
4	4.1	43	1.8
7	7.9	55	6.8
8	3.7	59	6.6
9	2.0	60	4.6
10	6.2	64	3.5
12	3.9	65	4.9
13	5.0	66	6.1
14	2.1	68	5.8
15	3.6	75	2.9
16	8.4	76	5.4
17	1.0	77	4.7
18	7.1	80	2.0
20	7.0	81	8.7
21	8.2	82	1.6
22	0.6	83	1.1
23	1.2	84	8.5
24	1.8	86	2.1
25	6.9	87	1.9
26	0.6	88	5.3
27	3.7	90	2.0
28	8.9	91	5.0
29	2.3	92	3.6
30	1.7	93	4.3
31	7.4		
33	8.5		
35	6.2		

産業上の利用可能性

本発明の新規スフィンゴシン誘導体は、脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防薬、治療薬として使用できる。

請求の範囲

1． 一般式（Ｉ）



［式中、Ｒ１は水素原子、Ｃ２－２０アルカノイル基、ベンゾイル基、「ハロゲン原子、Ｃ１－５アルキル基、水酸基、Ｃ１－５アルコキシ基、Ｃ２－５アルカノイル基、カルボキシル基、Ｃ２－５アルコキシカルボニル基、アミノ基、Ｃ１－５アルキル基の１若しくは２個で置換されたアミノ基、Ｃ２－５アルカノイルアミノ基、Ｃ２－５アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたＣ１－５アルキル基、シアノ基、ニトロ基、メルカプト基又はＣ１－５アルキルチオ基」で置換されたベンゾイル基、Ｃ４－８シクロアルキルカルボニル基、Ｃ２－２０アルコキシカルボニル基、式－ＣＯＣ(Ｒ３)２ＮＨＲ４（式中、Ｒ３は水素原子又はＣ１－５アルキル基であり、Ｒ４は水素原子又はＣ２－５アルコキシカルボニル基である。）で示される基又は式－ＣＯＣＯ２Ｒ３（式中、Ｒ３は水素原子又はＣ１－５アルキル基である。）で示される基であり、Ｒ２は水素原子、Ｃ１－８アルキル基、式－(ＣＨ２)ｎＲ５（式中、Ｒ５は水酸基、アミノ基、Ｃ１－５アルキル基の１～３個で置換されたアミノ基、カルボキシル基、Ｃ２－５アルコキシカルボニル基、カルバモイル基、Ｃ１－５アルキル基の１若しくは２個で置換されたアミノカルボニル基、カルバモイルオキシ基、Ｃ１－５アルキル基の１若しくは２個で置換されたアミノカルボニルオキシ基、フェニル基、「ハロゲン原子、Ｃ１－５アルキル基、水酸基、Ｃ１－５アルコキシ基、Ｃ２－５アルカノイル基、カルボキシル基、Ｃ２－５アルコキシカルボニル基、アミノ基、Ｃ１－５アルキル基の１若しくは２個で置換されたアミノ基、Ｃ２－５アルカノイルアミノ基、Ｃ２－５アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたＣ１－５アルキル基、シアノ基、ニトロ基、ウレイド基、Ｃ１－５アルキル基の１若しくは２個で置換されたウレイド基、メルカプト基又はＣ１－５アルキルチオ基」で置換されたフェニル基、ピリジル基、Ｃ１－５アルコキシ基で置換されたピ

リジル基、ピラジル基、ピロリジル基、ピペリジル基、ピペラジル基、モルホリニル基、チオモルホリニル基、イミダゾリル基、チアゾリル基、チアジアゾリル基、テトラゾリル基、キノリル基又は１Ｈ－インダゾリル基であり、ｎは０～５の整数である。）で示される基又は式－ＳＯｍＲ[6]（式中、Ｒ[6]はフェニル基又は「ハロゲン原子、Ｃ[1-5]アルキル基、水酸基、Ｃ[1-5]アルコキシ基、Ｃ[2-5]アルカノイル基、カルボキシル基、Ｃ[2-5]アルコキシカルボニル基、アミノ基、Ｃ[1-5]アルキル基の１若しくは２個で置換されたアミノ基、Ｃ[2-5]アルカノイルアミノ基、Ｃ[2-5]アルコキシカルボニルアミノ基、ハロゲン原子の１～５個で置換されたＣ[1-5]アルキル基、シアノ基、ニトロ基、ウレイド基、Ｃ[1-5]アルキル基の１若しくは２個で置換されたウレイド基、メルカプト基又はＣ[1-5]アルキルチオ基」で置換されたフェニル基であり、ｍは０、１又は２である。）で示される基であり、ＺはＮＲ[7]（ここで、Ｒ[7]は水素原子、水酸基又はＣ[1-5]アルキル基である。）であり、Ｙは酸素原子又はＮＲ[8]（Ｒ[8]は水素原子、水酸基又はＣ[1-5]アルキル基である。）であり、Ｗは酸素原子又は硫黄原子であり、ｋは１～２０の整数である。]で表わされるスフィンゴシン誘導体又はその薬学的に許容される塩。

２．　一般式（Ｉ）において、Ｒ[1]がイソブチリル基又はピバロイル基であり、Ｙが酸素原子であり、ＺがＮＨであり、ｋが１３である請求項１に記載のスフィンゴシン誘導体又はその薬学的に許容される塩。

３．　一般式（Ｉ）において、Ｒ[1]がイソブチリル基又はピバロイル基であり、Ｙ及びＺがＮＨであり、ｋが１３である請求項１に記載のスフィンゴシン誘導体又はその薬学的に許容される塩。

４．　請求の範囲１記載の化合物を有効成分とする、脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防または治療薬。

５．　請求の範囲１記載の化合物による、脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防または治療方法。

６．　脳出血や脳梗塞等の脳血管障害、頭部外傷、老人性痴呆、アルツハイマー病やパーキンソン氏病等の脳神経変性疾患、糖尿病、肥満、動脈硬化、炎症性疾患、免疫性疾患、ガン、腎疾患及び心疾患に対する予防または治療薬を製造するための、請求の範囲１記載の化合物の使用。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/08229

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C271/08, 271/12, 271/16, 271/20, 271/22, 271/28, 275/20, 275/42, 311/53, 323/43, C07D213/53, 213/75, C07D231/56, 233/61, 233/64, 241/20, 257/06, 277/46, 285/12, 295/12, A61K31/17, 31/27, 31/41, 31/416, 31/4164, 31/426,
Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C271/08, 271/12, 271/16, 271/20, 271/22, 271/28, 275/20, 275/42, 311/53, 323/43, C07D213/53, 213/75, C07D231/56, 233/61, 233/64, 241/20, 257/06, 277/46, 285/12, 295/12, A61K31/17, 31/27, 31/41, 31/416, 31/4164, 31/426,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN), MARPAT (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO, 95/21175, A1 (THE LIPOSOME COMPANY, INC.), 10 August, 1995 (10.08.95), Claims; pages 1 to 2 & AU, 9518712, A & EP, 742789, A1 & JP, 9-508900, A & KR, 97700679, A	1,2,4,6 3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January, 2001 (10.01.01)	23 January, 2001 (23.01.01)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/08229

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 5 pertains to methods for treatment of the human body by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/08229

Continuation of A
A61K31/433, 31/44, 31/4402, 31/4406, 31/4409, 31/4965, 31/5375,
A61P3/04, 3/10, 9/10, 13/12, 25/16, 25/28, 29/00, 35/00, A61P37/06

Continuation of B
A61K31/433, 31/44, 31/4402, 31/4406, 31/4409, 31/4965, 31/5375,
A61P3/04, 3/10, 9/10, 13/12, 25/16, 25/28, 29/00, 35/00, A61P37/06

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ００／０８２２９

Ａ．　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int. Cl.[7] C07C271/08, 271/12, 271/16, 271/20, 271/22, 271/28, 275/20, 275/42, 311/53, 323/43, C07D213/53, 213/75, C07D231/56, 233/61, 233/64, 241/20, 257/06, 277/46, 285/12, 295/12, A61K31/17, 31/27, 31/41, 31/416, 31/4164, 31/426, A61K31/433, 31/44, 31/4402, 31/4406, 31/4409, 31/4965, 31/5375, A61P3/04, 3/10, 9/10, 13/12, 25/16, 25/28, 29/00, 35/00,

Ｂ．　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int. Cl.[7] C07C271/08, 271/12, 271/16, 271/20, 271/22, 271/28, 275/20, 275/42, 311/53, 323/43, C07D213/53, 213/75, C07D231/56, 233/61, 233/64, 241/20, 257/06, 277/46, 285/12, 295/12, A61K31/17, 31/27, 31/41, 31/416, 31/4164, 31/426, A61K31/433, 31/44, 31/4402, 31/4406, 31/4409, 31/4965, 31/5375, A61P3/04, 3/10, 9/10, 13/12, 25/16, 25/28, 29/00, 35/00,

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS(STN), REGISTRY(STN), MARPAT(STN)

Ｃ．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X A	WO, 95/21175, A1(THE LIPOSOME COMPANY, INC.) 10.8月.1995 (10.08.95) 特許請求の範囲, 第1-2頁 &AU, 9518712, A &EP, 742789, A1 &JP, 9-508900, A &KR, 97700679, A	1, 2, 4, 6 3

☐ Ｃ欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー

「Ａ」特に関連のある文献ではなく、一般的技術水準を示すもの

「Ｅ」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの

「Ｌ」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）

「Ｏ」口頭による開示、使用、展示等に言及する文献

「Ｐ」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献

「Ｔ」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「Ｘ」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Ｙ」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「＆」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
１０．０１．０１	23.01.01

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）		
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	爾見　武志	４Ｈ	９５４７
	電話番号　０３－３５８１－１１０１　内線　３４４３		

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９８年７月）

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ００／０８２２９

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．[X] 請求の範囲 5 は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、
請求の範囲５は、人体の治療方法に関するものであるから、ＰＣＴ第17条(2)(a)(i)及びＰＣＴ規則39.1(iv)の規定により、この国際調査機関が調査をすることを要しない対象に係るものである。

2．[ ] 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3．[ ] 請求の範囲 _____ は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅱ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1．[ ] 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．[ ] 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．[ ] 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．[ ] 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

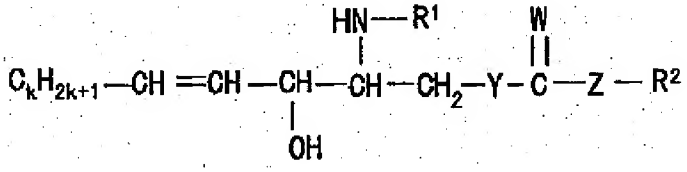
追加調査手数料の異議の申立てに関する注意
[ ] 追加調査手数料の納付と共に出願人から異議申立てがあった。
[ ] 追加調査手数料の納付と共に出願人から異議申立てがなかった。

第２ページＡ．欄の続き
A61P37/06

第２ページＢ．欄の続き
A61P37/06

CLAIMS

[Claim(s)]
[Claim 1]General formula (I)
[Formula 1]



R^1 among [type A hydrogen atom, C_{2-20} alkanoyl group, "Benzoyl, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, The benzoyl replaced by the cyano group, the nitro group, the sulfhydryl group, or C_{1-5} alkylthio group", C_{4-8} cycloalkyl carbonyl group, C_{2-20} alkoxycarbonyl group, Formula-$COC(R^3)_2NHR^4$ (among a formula, R^3 is a hydrogen atom or C_{1-5} alkyl group, and) R^4 is a hydrogen atom or C_{2-5} alkoxycarbonyl group. It is a basis shown by basis or formula-$COCO_2R^3$ (R^3 is a hydrogen atom or C_{1-5} alkyl group among a formula.) shown, R^2 is hydrogen atom, C_{1-8} alkyl group, and formula-$(CH_2)_nR^5$ (among a formula). The amino group by which R^5 was replaced by 1-3 pieces, a hydroxyl group, an amino group, and C_{1-5} alkyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, a carbamoyl group, The aminocarbonyl group replaced by 1 of C_{1-5} alkyl group, or two pieces, The aminocarbonyl oxy group replaced by 1 of a carbamoyloxy group and C_{1-5} alkyl group, or two pieces, "A phenyl group, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, The ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, The phenyl group replaced by the sulfhydryl group or C_{1-5} alkylthio group", A pyridyl group, the pyridyl group replaced by C_{1-5} alkoxy group, A pyrazyl group, a pyrrolidyl group, a piperidyl group, a PIPERAJIRU group, a morpholinyl group, A thiomorpholinyl group, an imidazolyl group, a thiazolyl group, a thiadiazolyl group, it is a tetrazolyl group, a quinolyl group, or a 1H-indazolyl group, and n is an integer of 0-5 -- basis [which is shown] or formula-SO_mR^6 (among a formula) R^6 A phenyl group or "halogen atom, C_{1-5} alkyl group, A hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, The ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, it is the phenyl group replaced by the sulfhydryl group or C_{1-5} alkylthio group", and m is 0, 1, or 2 -- it is a basis shown -- Z -- NR^7 (here) R^7 is a hydrogen atom, a hydroxyl group, or C_{1-5}

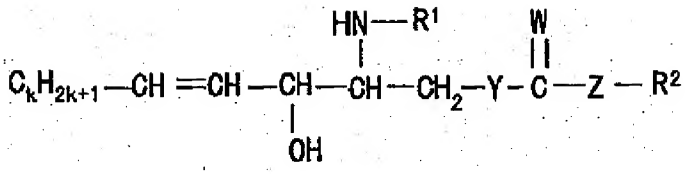
alkyl group. It is, Y is an oxygen atom or NR^8 (R^8 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group.), W is an oxygen atom or a sulfur atom, and k is an integer of 1-20. The sphingosine derivative expressed with], or its salt permitted pharmacologically.
[Claim 2]The sphingosine derivative according to claim 1 whose Y R^1 is an isobutyryl group or a pivaloyl group, and is an oxygen atom in general formula (I), whose Z is NH and whose k is 13, or its salt permitted pharmacologically.
[Claim 3]The sphingosine derivative according to claim 1 whose R^1 is an isobutyryl group or a pivaloyl group, Y and whose Z are NH(s) in general formula (I) and whose k is 13, or its salt permitted pharmacologically.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]Neutral sphingomyelinase is checked in this invention.
Therefore, it is related with a new sphingosine derivative useful as various medicines.

[0002]
[Description of the Prior Art]By using as a substrate sphingomyelin which is one of the sphingolipid which mainly exists in a cell membrane, sphingomyelinase is an enzyme disassembled into ceramide and the phosphocholine, and is divided roughly into an acid type and a neutral type from the optimal pH of the activity manifestation. Although a neutral type exists in a cell membrane or cytoplasm to an acid type carrying out localization to lysosome, both types are considered to participate in generation of the ceramide by the metabolic turnover of sphingomyelin.
[0003]The ceramide generated by sphingomyelinase has played the important role in various cell functions, such as apoptosis, cell growth, and differentiation, as a lipid second messenger, and this metabolic turnover production course is called the sphingomyelin course.
[0004]Sphingomyelinase The ischemia, TNF-alpha, IL-1beta, IFN-gamma, Since various stress, such as 1 alpha, 25-dihydroxy vitamin D_3, an anticancer agent, or radiation, is activated, it is possible that the sphingomyelin course is participating in the various symptoms chemical [these] and whose physical stress caused its onset and progress. For example, although a sphingomyelin course is activated at the time of brain ischemia, the sphingomyelinase to a brain-cell or addition of ceramide causes the cell death by apoptosis. Although production of TNF-alpha or IL-1beta rises at the time of brain ischemia and neuron death is induced, the solubilization receptor of TNF-alpha and the receptor antagonism agent of IL-1beta control the neuron death by the ischemia.

[0005]Production sthenia of TNF-alpha or IL-1beta is participating in cranial nerve degenerative diseases, such as head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, widely besides the above-mentioned cerebrovascular disease.
[0006]Although production of TNF-alpha in fat cells rises and insulin resistance is derived in non-insulin dependent diabetes mellitus and obesity, activation of the sphingomyelin course by TNF-alpha is participating in this. Although IL-1beta participates in the onset of insulin dependent diabetes mellitus, ceramide reveals the same operation as IL-1beta.
[0007]TNF-alpha and IL-1beta participates also in the process of the onset and progress of arteriosclerosis. That is, TNF-alpha and IL-1beta makes ICAM-1 of an adhesion factor reveal in a vascular endothelial cell, and promotes adhesion to a monocytic vascular endothelial cell, and the migration to the bottom of an inner bark. TNF-alpha causes the apoptosis of a vascular endothelial cell via activation of a sphingomyelin course. Activation of a sphingomyelin course promotes the LDL condensation by a vascular smooth muscle, and forms a lesion, and it destabilizes a plaque via the apoptosis of a vascular smooth muscle.
[0008]The physiology activity of the ceramide in an inflammation immune system cell is dramatically variegated, and is participating in the onset and progress of various inflammatory diseases and an immune disease deeply via derivation of differentiation and activation of a T cell and a B cell, various cytokine production, and apoptosis, production of an inflammatory prostagladin, etc. Since very much chemical and physical stress including TNF-alpha or IL-1beta participate in activation of a sphingomyelin course, it is thought that many cell lineage and signaling pathways are carrying out the cross talk to these symptoms intricately mutually.
[0009]From the above thing, specific inhibitor to sphingomyelinase, It can be used as the preventive medicine to cranial nerve degenerative diseases, such as cerebrovascular disease, such as cerebral hemorrhage and cerebral infarction, head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, diabetes mellitus, obesity, arteriosclerosis, an inflammatory disease, an immune disease, cancer, a renal disease, and a heart disease, and a remedy.
[0010]As a sphingosine derivative which has sphingomyelinase inhibitory action. Although 3-O-alkyl sphingomyelin is reported (Mark D.Lister, et al., Biochimica et Biophysica Acta, 1995, 1256, 25), the compound and chemical structure of this invention differ from each other.
[0011]
[Problem(s) to be Solved by the Invention]An object of this invention is to provide the new compound which has sphingomyelinase inhibitory action.
[0012]
[Means for Solving the Problem]In order to attain said technical problem, as a result of advancing research wholeheartedly, this invention persons found out that a certain kind of sphingosine derivative had neutral sphingomyelinase inhibiting activity, and completed this invention. That is, this invention is general formula (I).
[0013]
[Formula 2]



R^1 among [type A hydrogen atom, C_{2-20} alkanoyl group, "Benzoyl, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, Benzoyl replaced by cyano group, nitro group, sulfhydryl group, or C_{1-5} alkylthio group", C_{4-8} cycloalkyl carbonyl group, C_{2-20} alkoxycarbonyl group, Formula-$COC(R^3)_2NHR^4$ (among a formula, R^3 is a hydrogen atom or C_{1-5} alkyl group, and) R^4 is a hydrogen atom or C_{2-5} alkoxycarbonyl group. It is a basis shown by basis or formula-$COCO_2R^3$ (R^3 is a hydrogen atom or C_{1-5} alkyl group among a formula.) shown, R^2 is hydrogen atom, C_{1-8} alkyl group, and formula-$(CH_2)_nR^5$ (among a formula). An amino group by which R^5 was replaced by 1-3 pieces, a hydroxyl group, an amino group, and C_{1-5} alkyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, a carbamoyl group, An aminocarbonyl group replaced by 1 of C_{1-5} alkyl group, or two pieces, An aminocarbonyl oxy group replaced by 1 of a carbamoyloxy group and C_{1-5} alkyl group, or two pieces, "A phenyl group, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, An ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, A phenyl group replaced by sulfhydryl group or C_{1-5} alkylthio group", A pyridyl group, a pyridyl group replaced by C_{1-5} alkoxy group, A pyrazyl group, a pyrrolidyl group, a piperidyl group, a PIPERAJIRU group, a morpholinyl group, A thiomorpholinyl group, an imidazolyl group, a thiazolyl group, a thiadiazolyl group, it is a tetrazolyl group, a quinolyl group, or a 1H-indazolyl group, and n is an integer of 0-5 -- basis [which is shown] or formula-SO_mR^6 (among a formula) R^6 A phenyl group or "halogen atom, C_{1-5} alkyl group, A hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, An ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, it is the phenyl group replaced by sulfhydryl group or C_{1-5} alkylthio group", and m is 0, 1, or 2 -- it is a basis shown -- Z -- NR^7 (here) R^7 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group. It is, Y is an oxygen atom or NR^8 (R^8 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group.), W is an oxygen atom or a sulfur atom, and k is an integer of 1-20. They are a sphingosine derivative expressed with], or its salt permitted pharmacologically.

[0014]C_{2-20} alkanoyl group as used in this invention means a straight chain or a branched-chain

alkanoyl group with 2-20 carbon atoms, For example, an acetyl group, a propanoly group, isopropano yl groups, a butyryl group, an isobutyryl group, a valeryl group, a pivaloyl group, a milli styryl group, a stearyl group, etc. can be mentioned.
[0015]The number of carbon atoms means a thing of 2-5 among the above [C_{2-5} alkanoyl group].
[0016]C_{4-8} cycloalkyl carbonyl group means a cycloalkyl carbonyl group with 4-8 carbon atoms, for example, a cyclo propylcarbonyl group, a cyclopentyl carbonyl group, a cyclohexyl carbonyl group, a cycloheptyl carbonyl group, etc. can be mentioned.
[0017]C_{2-5} alkoxycarbonyl group means a straight chain or a branched-chain alkoxycarbonyl group with 2-5 carbon atoms, For example, a methoxycarbonyl group, an ethoxycarbonyl group, an ethoxycarbonyl group, a carbopropoxy group, a tert-butoxycarbonyl group, etc. can be mentioned.
[0018]C_{1-20} alkyl group means a straight chain or a branched-chain alkyl group with 1-20 carbon atoms, For example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, An isobutyl group, a tert-butyl group, a pentyl group, an isopentyl group, a hexyl group, an isohexyl group, a heptyl group, an octyl group, a nonyl group, a decyl group, a tridecyl group, a nonadecyl group, etc. can be mentioned.
[0019]C_{1-8} alkyl group means a thing with 1-8 carbon atoms among the above, and C_{1-5} alkyl group means a thing with 1-5 carbon atoms among the above.
[0020]An amino group replaced by 1-3 of C_{1-5} alkyl group means that a nitrogen atom of an amino group is replaced by C_{1-5} alkyl group, and means that it is the 4th class salt that three pieces are replaced.
[0021]C_{2-5} alkanoyl amino group means that a nitrogen atom of an amino group is replaced by one of C_{2-5} alkanoyl group, for example, an acetylamino group, an isopropionylamino group, etc. can be mentioned.
[0022]C_{2-5} alkoxycarbonylamino group means that a nitrogen atom of an amino group is replaced by one of C_{2-5} alkoxycarbonyl group, for example, a methoxycarbonylamino group, a butoxycarbonylamino group, etc. can be mentioned.
[0023]A halogen atom is a fluorine atom, a chlorine atom, a bromine atom, or iodine atoms. C_{1-5} alkyl group replaced by 1-5 of a halogen atom means a straight chain or a branched-chain alkyl group with 1-5 carbon atoms replaced with said halogen atom, for example, a trifluoromethyl group etc. can be mentioned.
[0024]C_{1-5} alkoxy group means a straight chain or a branched-chain alkoxy group with 1-5 carbon atoms, for example, a methoxy group, an ethoxy basis, a propoxy group, an isopropoxy group, a butoxy group, a heptoxy group, etc. can be mentioned.
[0025]C_{1-5} alkylthio group means a straight chain or a branched-chain alkylthio group with 1-5 carbon atoms, For example, a methylthio group, an ethyl thio group, a propyl thio group, an isopropyl thio group, a butyl thio group, an isobutyl thio group, a tert-butyl thio group, a pentyl thio group, a hexyl thio group, etc. can be mentioned.
[0026]As a protective group of a hydroxyl group, acetal type protective groups, such as 3

substitution silyl group; tetrahydropyranyloxy groups, such as acyl group; trimethylsilyl groups, such as an acetyl group and benzoyl, t-butyldimethylsilyl group, and a benzyl dimethylsilyl group, and a methoxymethyl group, etc. can be mentioned.

[0027]When a substituent expressed with two or more same signs in one general formula exists, they may be the same or may differ.

[0028]Salts permitted pharmacologically show acid or alkali addition salt. In this case, although there is no restriction in particular in acid or alkali to be used, as acid, chloride, sulfuric acid, nitric acid, acetic acid, benzenesulfonic acid, etc. can be mentioned, and ammonium ion, such as metal ions, such as sodium and potassium, and alkylammonium, etc. can be mentioned as alkali.

[0029]A compound of this invention may be a single optically active substance, or may be a mixture of a stereoisomeric form.

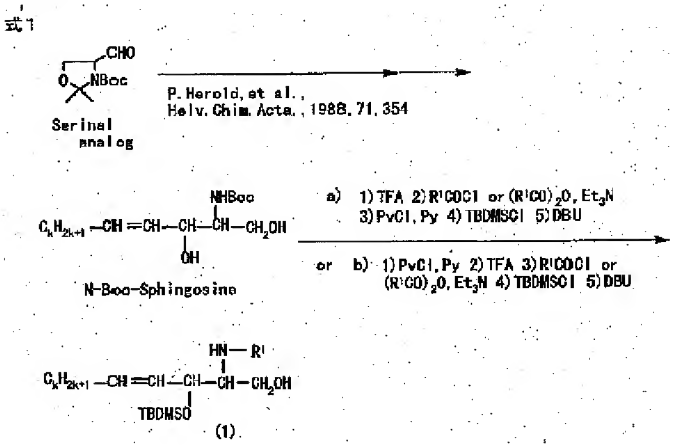
[0030]A compound of this invention can be manufactured in accordance with a method shown below, for example.

[0031]In this specification, Boc hereafter A tert-butoxycarbonyl group, As for TFA, a pivaloyl group and DBU trifluoroacetic acid and Pv 1,8-diazabicyclo[5.4.0]undec-7-ene, As for TCF, chloroformic acid trichloromethyl and TBDMS express a tert-butyldimethylsilyl group, WSC-HCl expresses a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, and HOBt may express 1-hydroxybenzotriazol, respectively.

[0032]First, N-Boc-sphingosine which is synthetic powder can be compounded from serinal in accordance with a method (Helv.Chim.Acta., 1988, 71,354) of P.Herold and others, and can compound an intermediate compound (1) by a method subsequently to the formula 1 shown.

[0033]

[Formula 3]



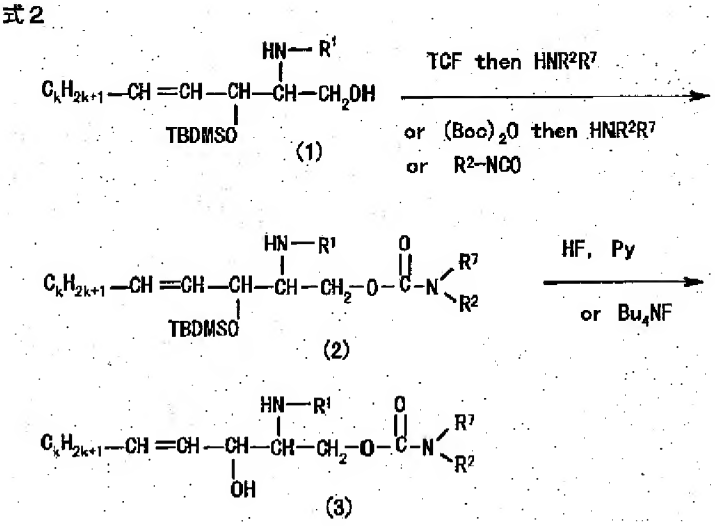
In the compound of general formula (I), the compound (3) Y and whose W are oxygen atoms and whose Z is NR^7 can be manufactured by the method shown in the formula 2. That is, after processing a compound (1) for bottom chloroformic acid trichloromethyl of base existence, or 2 di-tert-butyl carbonate, a compound (2) can be obtained by making it react to a corresponding amine compound. A compound (2) can also be obtained by making an intermediate (1) react to a corresponding isocyanate. A compound (3) can be obtained by desilanizing a compound (2) with

hydrofluoric acid or tetrabutylammonium fluoride. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0034]

[Formula 4]

式2

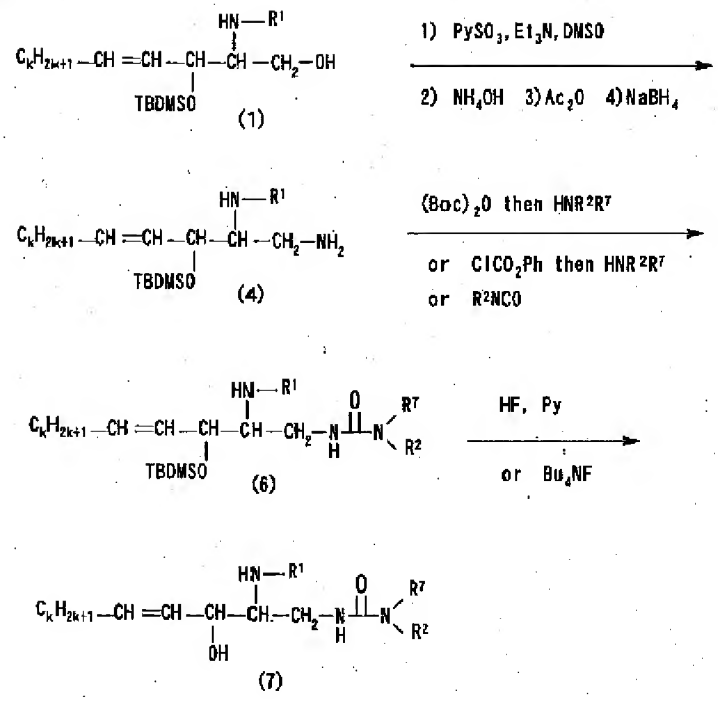


In the compound of general formula (I), the compound (7) whose Y is NH, whose W is an oxygen atom and whose Z is NR^7 can be manufactured by the method shown in the formula 4. Namely, after oxidizing by a sulfur trioxide pyridine complex and triethylamine and using a compound (1) as an aldehyde object among dimethyl sulfoxide, It was made to react to hydroxylamine and an acetic anhydride one by one, the generated acetoxyimine object was returned with sodium borohydride, and it changed into the amine compound (4). Although the example using TBDMS as a protective group of a hydroxyl group is shown in the formula 3, other amine compounds can be manufactured using other above-mentioned protective groups or by carrying out deprotection on condition of common use. Subsequently, after processing a compound (4) for chloroformic acid phenyl or 2 di-tert-butyl carbonate, a compound (6) can be obtained by making it react to a corresponding amine compound. A compound (6) can also be obtained by making a compound (4) react to a corresponding isocyanate. A compound (7) can be obtained by desilanizing a compound (6). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0035]

[Formula 5]

式4

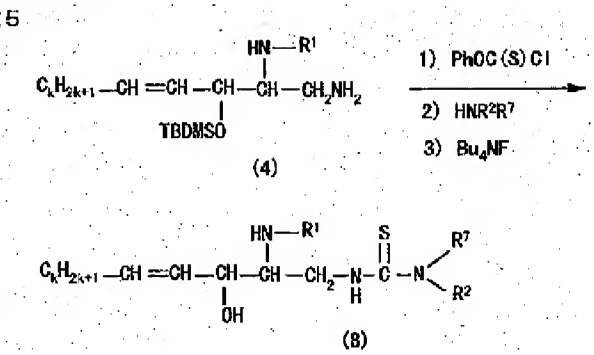


In the compound of general formula (I), the compound (8) whose Y is NH, whose W is a sulfur atom and whose Z is NR^7 can be manufactured by the method shown in the formula 5. That is, a compound (8) can be obtained by making a compound (4) react to the isothiocyanate which makes it react to chloro CHIONO formic acid phenyl and an amine compound corresponding after a reaction, or corresponds, and desilanizing it further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0036]

[Formula 6]

式5

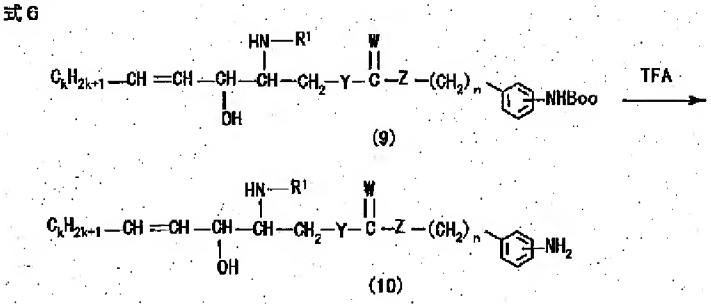


In the compound of general formula (I), the compound (10) and compound (11) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (phenyl group by which R^5 was replaced with the amino group or $C_{2\text{-}5}$ alkanoyl amino group), It can manufacture by the method shown in the formula 6. That is, trifluoroacetic acid removes Boc for the compound (9) obtained by one which is shown

by said formulas 2-5 of methods, and a compound (10) is obtained. When considering it as an acetylamino group, it can change into a compound (11) by making it react to an acetic anhydride further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0037]

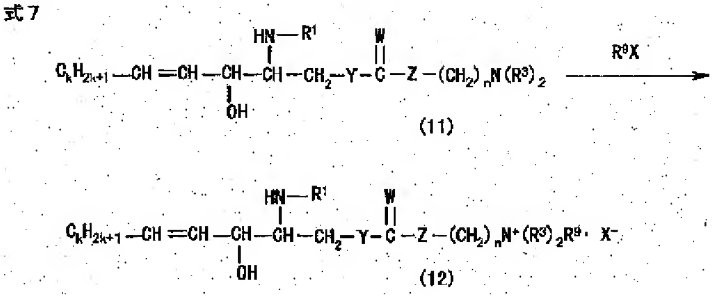
[Formula 7]



In the compound of general formula (I), R^2 can manufacture the compound (13) which is a basis shown by formula-$(CH_2)_nR^5$ (R^5 is the 4th class amine) by the method shown in the formula 7. That is, a compound (13) can be obtained by making the compound (12) obtained by one which is shown by said formulas 2-5 of methods react to corresponding alkyl halide. Reaction conditions, such as a reagent in this reaction, time, temperature, and a solvent, can be performed on the conditions usually used.

[0038]

[Formula 8]

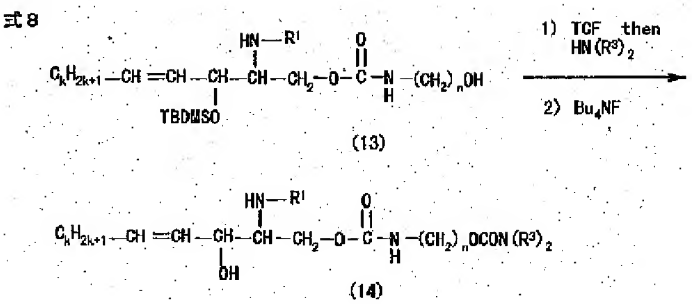


(R^9 shows C_{1-5} alkyl group among a formula, and X shows a halogen atom.) In the compound of general formula (I), The compound (15) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (aminocarbonyl oxy group with which R^5 was replaced by 1 of a carbamoyloxy group or C_{1-5} alkyl group, or two pieces), It can manufacture by the method shown by the formula 8. That is, after processing the compound (14) obtained by one which is shown by said formulas 2-5 of methods by chloroformic acid trichloromethyl, a compound (15) can be obtained by making it react to a corresponding amine compound, and desilanizing further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0039]

[Formula 9]

式 8



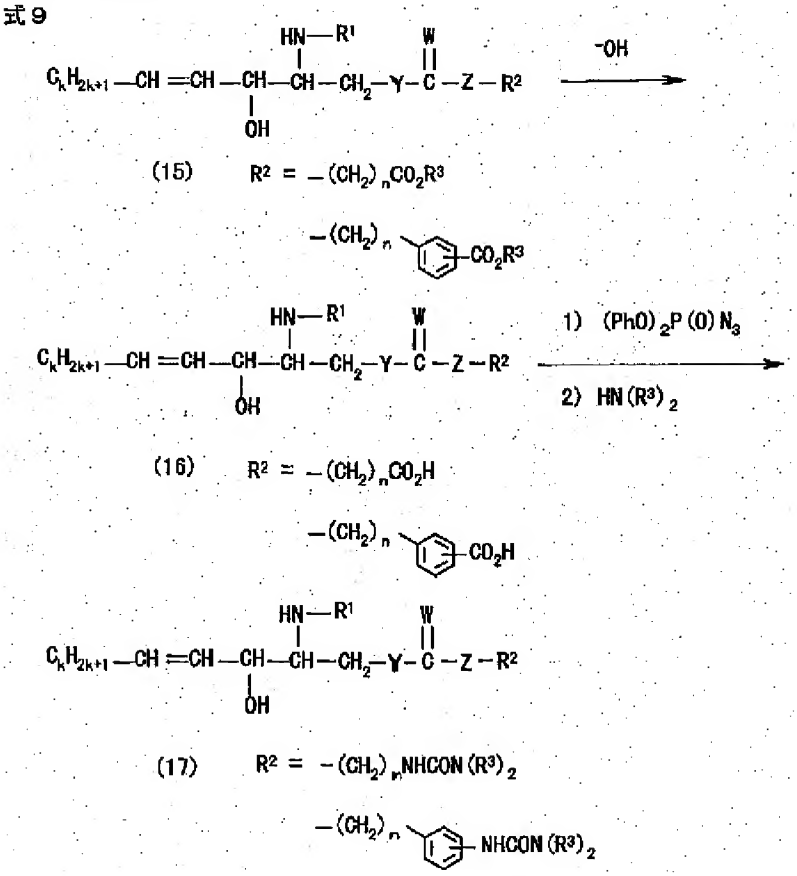
In the compound of general formula (I), the compound (17) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (phenyl group by which R^5 was replaced by the carboxyl group or the carboxyl group), As the formula 9 showed, the compound (16) obtained by one which is shown by said formulas 2-5 of methods can be hydrolyzed by the usual method of hydrolyzing ester.

[0040]After processing a compound (17) by diphenylphosphoric acid azide, a compound (18) can be obtained by making it react to a corresponding amine compound. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0041]

[Formula 10]

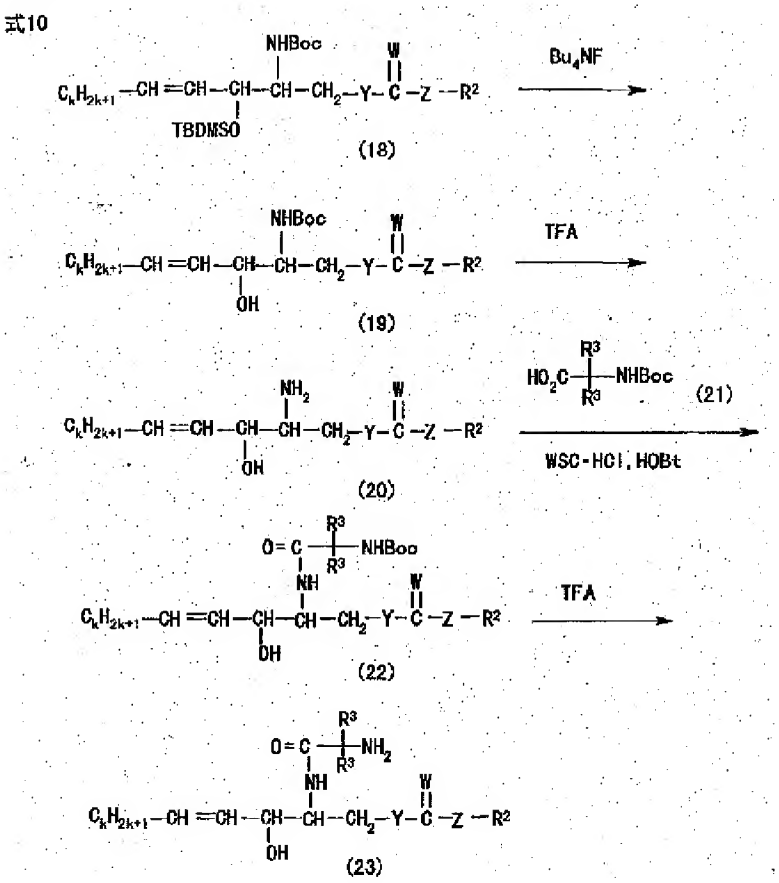
式 9



As shown in the formula 10, a compound (20) can be obtained by desilanizing the compound (19) led from N-Boc-sphingosine. Subsequently, the compound (20) obtained here can be processed with trifluoroacetic acid, and a compound (21) can be obtained. A compound (23) can be obtained by condensing a compound (21) and an amino acid derivative (22). A compound (23) can be processed with trifluoroacetic acid and can be changed into a compound (24). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0042]

[Formula 11]

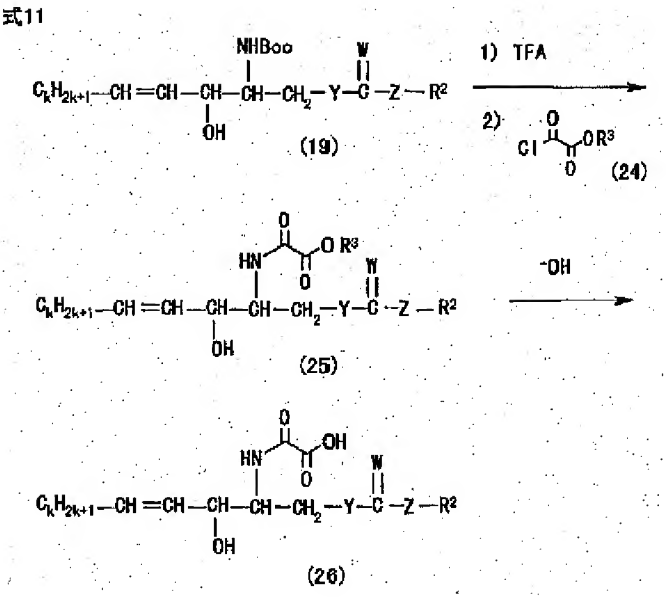


As shown in the formula 11, a compound (25) can be obtained by making a compound (21) react to the halide of a compound (27). It is convertible for a compound (26) by hydrolyzing a compound (25). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0043]

[Formula 12]

式11



[Effect of the Invention]The new sphingosine derivative of this invention Cerebrovascular disease, such as cerebral hemorrhage and cerebral infarction, It can be used as the preventive medicine to cranial nerve degenerative diseases, such as head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, diabetes mellitus, obesity, arteriosclerosis, an inflammatory disease, an immune disease, cancer, a renal disease, and a heart disease, and a remedy.

[0044]

[Example]Hereafter, a reference example, an example, and the example of an examination are given, and this invention is explained still in detail.

[0045]2-N-(tert-butoxycarbonyl)-D-erythro sphingosine was manufactured according to the method given in literature (P. Herold, et al., Helv.Chim.Acta., 1988, 71,354).

[0046]The ^{1}H-NMR-spectrum value described below was measured at 200 MHz (when there is no statement in particular).

At the dichloromethane (60 ml) solution of reference example 12-N-(tert-butoxycarbonyl)-D-erythro sphingosine (5.6 g,14mmol), the bottom trifluoroacetic acid (12 ml) of -20 ** cooling was dropped, and temperature up was carried out to the room temperature over 3 hours to it. The solvent was distilled off, and to the residue, hydrous methanol (water: methanol =12ml:200ml) and after adding potassium carbonate (3.8g) subsequently, it stirred at the room temperature for 24 hours. Column chromatography refined the residue after distilling off a solvent, and D-erythro sphingosine (5.5g) was obtained.

[0047]The compound obtained here was dissolved in the tetrahydrofuran (60 ml), the bottom triethylamine of ice-cooling (5.1 ml, 37mmol) was added, and, subsequently pivaloyl chloride (1.8 ml, 15mmol) was dropped. After stirring under the temperature for 1 hour, saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. After desiccation and a solvent were distilled off for the extract with magnesium sulfate, column chromatography

refined the residue, and 2-N-pivaloyl D-erythro sphingosine (3.4g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.08-1.47(m,22H),1.21(s,9H),1.95-2.13(m,2H),2.83-3.07(m,2H),3.69(m,1H),3.78-4.02(m, 2H, 4.29(m,1H),5.51(dd,J=6.5,15.4Hz,1H),5.77(dt,J=15.4,6.9Hz,1H),6.42(d,J=6.8Hz,1H) [0048]The compound (0.90 g, 2.3mmol) obtained by the reference example 2 reference example 1 was melted in pyridine (8 ml), pivaloyl chloride (0.35 ml) was dropped under -10 ** cooling, and it stirred under the temperature for 3 hours. After adding water to reaction mixture, ethyl acetate extracted and it dried with magnesium sulfate. The solvent was distilled off, column chromatography refined the residue and 2-N and 1-O-dipivaloyl D-erythro sphingosine (0.90g) were obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.19(s,9H),1.20(s,9H),1.23-1.42(m,22H),1.99-2.10(m,2H),3.09(bs,1H),4.14(dd,J=3.9, 11.4Hz,1H),4.17(m,1H),4.24(m,1H),4.34(dd,J=7.0,11.4Hz,1H),5.46(ddt,J=6.6,15.4,1.3Hz,1H),5.75(ddt,J=0.9, 15.4, 1.3 Hz, 1H, 6.09(d,J=7.6Hz,1H)[0049]The compound (2.3 g, 5.0mmol) obtained by the reference example 3 reference example 2 is melted in N.N-dimethylformamide (10 ml), Imidazole (2.72 g, 10mmol) was added, subsequently tert-butyldimethylsilyl chloride (2.7 g, 18mmol) was added, and it stirred at 60 ** for 17 hours. After condensing reaction mixture by decompression, column chromatography refined the residue and 3-O-(tert-butyldimethylsilyl)-2-N and 1-O-dipivaloyl D-erythro sphingosine (2.8g) were obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm) : 0.01(s,3H),0.04(s,3H),0.88(t,J=6.7Hz,3H),0.88(s,9H),1.15(s,9H),1.16(s,9H),1.22-1.38(m,22H),1.93-2.04(m, 2H),3.29(dd,J=4.6,9.0Hz,1H),3.63(dd,J=3.6,9.0Hz,1H),3.91(m,1H),4.17(dd,J=6.7,7.4Hz,1H),5.42(dd,J=7.4,15.4Hz, 1H, 5.57(dt,J=15.4,6.7Hz,1H),5.91(d,J=8.6Hz,1H) [0050]The output (2.8 g, 4.8mmol) acquired by the reference example 4 reference example 3 was melted in non-aqueous methanol (30 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.68 g, 4.5mmol) was added, and it stirred for three days at the room temperature. Reaction mixture was condensed by decompression, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (2.2g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm):0.03(s,3H),0.06(s,3H),0.87(t,J=6.5Hz,3H),0.90(s,9H),1.02-1.44(m,22H),1.15(s,9H),1.93-2.11(m,2H),3.42(d, J=9.8Hz,1H),3.56(ddd,J=3.0,9.8,11.0Hz,1H),3.76(m,1H),4.00(dd,J=2.3,11.0Hz,1H),4.42(m,1H), 5.44(dd,J=6.3-15.4Hz, 1H, 5.76(dt,J=15.4,6.6Hz,1H),6.52(d,J=7.0Hz,1H) [0051]Reference example 52-N-(tert-butoxycarbonyl)-D-erythro sphingosine (2.0 g, 5.0mmol) was melted in pyridine (20 ml), and pivaloyl chloride (0.66 g, 5.5mmol) was dropped under -20 ** cooling. After returning reaction mixture to a room temperature over 2 hours, saturated sodium bicarbonate water was added and ethyl acetate extracted. The solvent was distilled off for the extract after desiccation with magnesium sulfate, column chromatography refined the residue, and 2-N-(tert-butoxycarbonyl)-1-O-pivaloyl D-erythro sphingosine (2.2g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.9Hz,3H),1.21(s,9H),1.21-

1.41(m,22H),1.44(s,9H),2.00-2.08(m,2H),2.33(bs,1H),3.94(m,1H),4.12(dd, J=4.4,11.4Hz,1H),4.15(m,1H),4.26(dd,J=6.6,11.4Hz,1H),4.80(bd,J=7.8Hz,1H),5.49(dd,J=6.8,15.4Hz,1H),5.75 (dt, J= 15.4, 6.8 Hz, 1H) [0052]The compound (2.2 g, 4.5mmol) obtained by the reference example 5 was added to reference example 6 trifluoroacetic acid (14 ml) under ice-cooling, and temperature up was carried out to the room temperature over 3 hours. After condensing reaction mixture by decompression, ethanol was added and it condensed again. The residue was melted in the tetrahydrofuran (14 ml), the bottom triethylamine of ice-cooling (1.4 g, 14mmol) was added, subsequently the isobutyric anhydride (0.85 g, 5.4mmol) was added, and it stirred under the temperature for 1.5 hours. Ethyl acetate extracted, after adding water to reaction mixture. It condensed, after drying an extract with sodium sulfate. Melt a residue in N.N-dimethylformamide (14 ml), and imidazole (1.6 g, 24mmol) is added, Subsequently, tert-butyldimethylsilyl chloride (1.2 g, 8.1mmol) was added, and it stirred at the room temperature for 8 hours, and water was added after concentration under decompression and ethyl acetate extracted reaction mixture. The solvent was distilled off after desiccation with sodium sulfate, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl 1-O-pivaloyl D-erythro sphingosine (2.3g) was obtained.

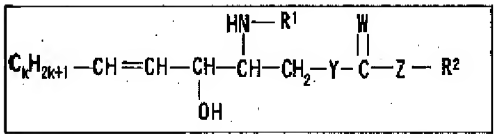
[0053]The compound (2.3 g, 4.0mmol) obtained here was melted in drying methanol (30 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.92 g, 6.4mmol) was added, and it stirred at the room temperature for 28 hours. Reaction mixture was condensed by decompression, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (1.9g) was obtained.

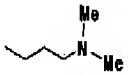
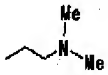
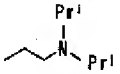
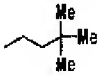
^{1}H-NMR ($CDCl_3$) delta (ppm):0.02 (s, 3H), 0.05 (s, 3H), 0.85 (t, J= 6.7 Hz, 3H), 0.89 (s, 9H), 1.13. (d, J= 6.8 Hz, 6H), 1.08-1.44(m,22H),1.94-2.14(m,2H),2.38(m,1H),3.31(m,1H),3.54(m,1H),3.77(m,1H),4.01(dd,J=3.0,11.3Hz,1H), 4.42(dd,J=2.9,6.0Hz,1H),5.44(dd,J=6.2,15.4Hz,1H),5.71(dt,J=15.4,6.8Hz,1H),6.29(d,J=7.4Hz,1H) [0054]The compound of this invention manufactured in Example 104 from the following Examples 1 was shown in the following tables.

[0055]

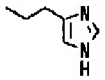
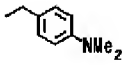
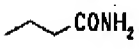
[Table 1]

表1

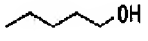
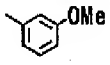
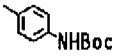
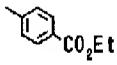
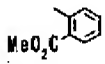
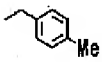
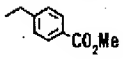


実施例	k	R^1	R^2	Y	Z	W
1	13	tBuCO	H	O	NH	O
2	13	tBuCO	OH	O	NH	O
3	13	tBuCO		O	NH	O
4	13	tBuCO		O	NH	O
5	13	tBuCO		O	NH	O
6	13	tBuCO		O	NH	O
7	13	tBuCO		O	NH	O
8	13	tBuCO		O	NH	O
9	13	tBuCO		O	NH	O
10	13	tBuCO		O	NH	O
11	13	tBuCO		O	NH	O
12	13	tBuCO		O	NH	O
13	13	tBuCO		O	NH	O
14	13	tBuCO		O	NH	O

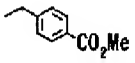
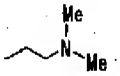
[Table 2]

実施例	k	R^1	R^2	Y	Z	W
15	13	tBuCO		O	NH	O
16	13	tBuCO		O	NH	O
17	13	tBuCO		O	NH	O
18	13	tBuCO		O	NH	O
19	13	PhCO		O	NH	O
20	13	tBuCO		O	NH	O
21	13	tBuCO		O	NH	O
22	13	tBuCO		O	NH	O
23	13	tBuCO		O	NH	O
24	13	tBuCO		O	NH	O
25	13	tBuCO		O	NH	O
26	13	tBuCO		O	NH	O
27	13	tBuCO		O	NH	O
28	13	iPrCO	H	O	NH	O
29	13	iPrCO		O	NH	O
30	13	iPrCO		O	NH	O

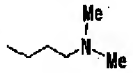
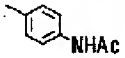
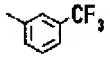
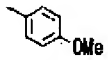
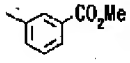
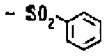
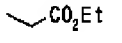
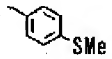
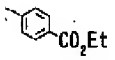
[Table 3]

実施例	k	R^1	R^2	Y	Z	W
31	13	iPrCO		O	NH	O
32	13	iPrCO		O	NH	O
33	13	iPrCO		O	NH	O
34	13	iPrCO		O	NH	O
35	13	iPrCO		O	NH	O
36	13	iPrCO		O	NH	O
37	13	iPrCO		O	NH	O
38	13	iPrCO		O	NH	O
39	13	iPrCO		O	NH	O
40	13	iPrCO		O	NH	O
41	13	iPrCO		O	NH	O
42	13	iPrCO		O	NH	O
43	13	iPrCO		O	NH	O
44	13	iPrCO		O	NH	O
45	13	iPrCO		O	NH	O
46	13	iPrCO		O	NH	O

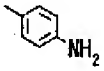
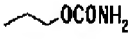
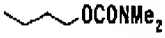
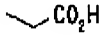
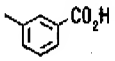
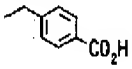
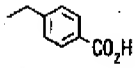
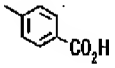
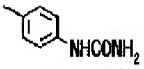
[Table 4]

実施例	k	R^1	R^2	Y	Z	W
47	13	iPrCO		O	NH	O
48	13	iPrCO		O	NH	O
49	13	iPrCO		O	NH	O
50	13	iPrCO		O	NH	O
51	13	iPrCO		O	NOH	O
52	1	$C_{13}H_{27}CO$		O	NH	O
53	6	iPrCO		O	NH	O
54	6	$C_{17}H_{35}CO$		O	NH	O
55	10	iPrCO		O	NH	O
56	10	iPrCO		O	NH	O
57	10	iPrCO	H	O	NH	O
58	10	iPrCO		O	NH	O
59	15	tBuCO		O	NH	O
60	15	tBuCO	H	O	NH	O
61	13	$C_{17}H_{35}CO$		O	NH	O
62	13	MeCO	H	O	NH	O

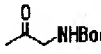
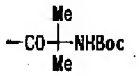
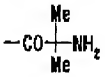
[Table 5]

実施例	k	R^1	R^2	Y	Z	W
63	13	tBuCO		O	NMe	O
64	13	iPrCO		O	NH	O
65	13	iPrCO	Me	O	NH	O
66	13	iPrCO		O	NH	O
67	13	iPrCO		O	NH	O
68	13	iPrCO		O	NH	O
69	13	iPrCO		O	NH	O
70	13	iPrCO		O	NH	O
71	13	tBuCO		O	NH	O
72	13	tBuCO		O	NH	O
73	13	iPrCO		O	NH	O
75	13	tBuCO		NH	NH	O
76	13	tBuCO	H	NH	NH	O
77	13	tBuCO	Me	NH	NH	O
78	13	tBuCO		NH	NH	O

[Table 6]

実施例	k	R^1	R^2	Y	Z	W
79	13	tBuCO		NH	NH	S
80	13	iPrCO		O	NH	O
81	13	tBuCO		O	NH	O
82	13	tBuCO		O	NH	O
83	13	tBuCO		O	NH	O
84	13	iPrCO		O	NH	O
85	13	tBuCO		O	NH	O
86	13	tBuCO		O	NH	O
87	13	iPrCO		O	NH	O
88	13	iPrCO		O	NH	O
89	13	iPrCO		O	NH	O
90	13	iPrCO		O	NH	O
91	10	iPrCO		O	NH	O
92	13	tBuCO		NH	NH	O
93	13	tBuCO		NH	NH	O
94	13	Boc	H	O	NH	O

[Table 7]

実施例	k	R^1	R^2	Y	Z	W
95	13	Boc		O	NH	O
96	13	H	H	O	NH	O
97	13	H		O	NH	O
98	13	H		O	NH	O
99	13			O	NH	O
100	13			O	NH	O
101	13			O	NH	O
102	13			O	NH	O
103	13			O	NH	O
104	13			O	NH	O

Example 13-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (99 mg, 0.2mmol) was melted in dichloromethane (5 ml), pyridine (142 mg, 1.8mmol) was added, and it cooled at -78 **. After chloroformic acid trichloromethyl (22microl, 0.3mmol) was dropped at this solution, temperature up was carried out to -15 ** over 1 hour. The ammonia solution (2 ml) was dropped at this reaction mixture 25%, and temperature up was carried out to it to 15 ** over 3 hours. Water was added to reaction mixture, ethyl acetate extracted, and the solvent was distilled off after drying with magnesium sulfate. Column chromatography refined the residue and 3-O-(tert-butyldimethylsilyl)-1-O-carbamoyl 2-N-pivaloyl D-erythro sphingosine (72 mg) was obtained.

[0056]After melting the compound (72 mg, 0.13mmol) obtained here in pyridine (6 ml) and adding the acetonitrile (34 ml) solution of hydrofluoric acid bottom 2% of ice-cooling, it stirred for seven days at the room temperature. After it added saturated sodium bicarbonate water to reaction mixture and ethyl acetate subsequently extracted, it dried with magnesium sulfate. The solvent was distilled off, column chromatography refined the residue and 1-O-carbamoyl 2-N-pivaloyl D-erythro sphingosine (51 mg) was obtained.

^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.19(s,9H),1.21-1.40(m,22H),2.03(m,2H),3.34(d,J=5.1Hz,1H),4.10(dd,J=3.8,11.8Hz,1H), 4.14(m,1H),4. 21 (m, 1H), 4.41 (dd, J= 7.6-11.7 Hz, 1H), 4.74 (bs, 2H), 5.45 (dd, J= 6.7-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.7 Hz, 1H) and 6.29(d, J= 7.5-Hz, 1H)MS (SIMS) m/e:427$(M+H)^+$$C_{24}H_{46}N_2O_4$ (426)

[0057]The compound of Examples 2-63 was manufactured like the method of two to example 63

Example 1. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown below. Compound ^{1}H-NMR of Example 2. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.19(s,9H),1.20-1.43(m,22H),2.04(m,2H),2.71(d,J=4.5Hz,1H),4.19(d,J=5.3Hz,1H),4.24(m, 1H),4.30(dd,J=3,6,11.5Hz,1H),4.43(dd,J=7.8,11.6Hz,1H),5.47(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz, 1H, 6.05 (bs, 1H), 6.21 (d, J= 7.8 Hz, 1H) and 7.19(bs, 1H)MS(SIMS) m/e:505 $^{(M+Na)+}C_{28}H_{48}0_4$ (504) [0058]Compound ^{1}H-NMR of Example 3. ($CDCl_3$) delta. (ppm) : 0.88(t,J=7.0Hz,3H),1.17(s,9H),1.20-1.42(m,22H),1.90-2.08(m,4H),2.93(s,6H),3.16-3.34(m,4H),4.14(m,2H), 4.30 (m, 1H), 5.44 (dd, J= 6.7-15.3 Hz, 1H), 5.77 (dt, J= 15.3, 6.7 Hz, 1H), 6.05 (m, 1H) and 6.32(d, J= 8.0-Hz, 1H)MS(SIMS) m/e:512 $^{(M+H)+}C_{29}H_{57}N_30_4$ (511) [0059]Compound ^{1}H-NMR of Example 4. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,1H),1.20(s,9H),1.22-1.40(m,22H),2.03(m,2H),2.82(s,6H),3.14(m,2H),3.45(m,1H),3.57(m,1H), 4.12-4.34 (m, 2H), 5.49 (dd, J= 6.4-15.3 Hz, 1H), 5.78 (dt, J= 15.3, 6.7 Hz, 1H), 5.92 (m, 1H), and 6.47(d, J= 7.6-Hz, 1H)MS(SIMS) m/e:498 $^{(M+H)+}C_{28}H_{55}N_30_4$ (497) [0060]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.7], 3H) of Example 5, 1.01 (d,J=6.4Hz,12H),1.18(s,9H),1.20-1.40(m,22H),2.02(m,2H),2.58(m,2H),3.01(m,2H),3.15(m,2H),3.78(m,1H),4. 01-4.26 (m, 3H), 4.42 (dt, J= 6.7-11.8 Hz, 1H), 5.44 (dd, J= 6.6-15.4 Hz, 1H), and 5.72(dt, J= 15.3, 6.7-Hz, 1H)MS(SIMS) m/e:554 $^{(M+H)+}C_{32}H_{63}N_3O_4$ (553) [0061]Compound ^{1}H-NMR of Example 6. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),0.92(s,9H),1.19(s,9H),1.20-1.40(m,22H),1.41(m,2H),2.02(m,2H),3.05-3.25(m,2H),3.68(d, J=5.5Hz,1H),3.95-4.30(m,3H),4.42(dd,J=7.4,11.7Hz,1H),4.70(m,1H),5.44(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4, 6.6 Hz, 1H, 6.41(d, J= 7.1-Hz, 1H)MS(SIMS) m/e:511 $^{(M+H)+}C_{30}H_{58}N_2O_4$ (510) [0062]Compound ^{1}H-NMR of Example 7. ($CDCl_3$) delta(ppm):0.88(t,J=6.5Hz,3H),1.17(s,9H),1.20-1.42(m,22H),2.02(m,2H),3.19(m,1H),4.19(m,1H),4.22-4.32(m,2H),4.52(dd, J=8.0,12.7Hz,1H),5.49(dd,J=6.7,15.4Hz,1H),5.76(dt,J=15.3,6.8Hz,1H),6.22(d,J=7.4Hz,1H),7.02(m,1H),7.70(m, 1H, 7.94 (m, 1H), 8.13 (bs, 1H) and 8.27(m, 1H)MS(SIMS) m/e:504$(M+H)^+C_{29}H_{49}N_3O_4$ (503) [0063]Compound ^{1}H-NMR of Example 8. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.04(m,2H),4.21(m,1H),4.27-4.35(m,2H),4.52(dd,J=8.2,12. 4Hz,1H),5.50(dd,J=6.7,15.4Hz,1H),5.78(dt,J=15.4,6.5Hz,1H),6.17(d,J=7.8Hz,1H),7.45(bs,1H),8.22(m,1H),8.32 (m, 1H), 9.29(m, 1H)MS(SIMS) m/e:505 $^{(M+H)+}C_{28}H_{48}N_4O_4$ (504) [0064]Compound ^{1}H-NMR of Example 9. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),4.15-4.40(m,3H),4.50(dd,J=7.5,10.9Hz,1H),5. J= 6.3 Hz of 49(dd,J=6.5,15.4Hz,1H),5.78(dt,J=15.4,6.6Hz,1H),6.19(d,J=7.7Hz,1H),7.35(d,J=6.3Hz,1H),7.48(s,1H),8.47(d, 1HMS(SIMS) m/e:504 $^{(M+H)+}C_{29}H_{49}N_3O_4$ (503) [0065]Compound ^{1}H-NMR of Example 10. ($CDCl_3$) delta(ppm):0.88(t,J=7.1Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),3.91(s,3H),4.12-4.33(m,3H),4.50(dd,J=4.7,12. 4Hz,1H),5.47(dd,J=6.5,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.25(bd,J=6.2Hz,1H),6.73(d,J=8.9

Hz,1H),6.78(bs, 1H, 7.75 (bs, 1H) and 8.09(bs, 1H)MS(SIMS) m/e:534 $^{(M+H)^+}C_{29}H_{49}N_3O_4$ (533)
[0066]Compound ^{1}H-NMR of Example 11. ($CDCl_3$)
delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-
1.40(m,22H),2.03(m,2H),2.82(d,J=4.1Hz,1H),4.27(m,2H),4.43(dd,J=2.
6,11.2Hz,1H),4.62(dd,J=3.6,11.1Hz,1H),5.54(J=6.3,15.3Hz,1H),5.78(dt,J=15.4,6.7Hz,1H),6.47(
d,J=7.6Hz, 1H, 8.77 (s, 1H), 12.2(bs, 1H)MS(SIMS) m/e:511$(M+H)^+C_{26}H_{46}N_4O_4S$ (510)
[0067]Compound ^{1}H-NMR of Example 12. ($CDCl_3$)
delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-
1.40(m,22H),2.03(m,2H),3.12(d,J=3.1Hz,1H),4.20(m,1H),4.22(dd,J=3.
9,11.8Hz,1H),4.31(m,1H),4.53(dd,J=7.7,11.7Hz,1H),5.49(dd,J=6.6,15.4Hz,1H),5.77(dt,J=15.3,6.
7Hz,1H),6.
28(d,J=7.2Hz,1H),6.93(bs,1H),7.30(d,J=8.5Hz,1H),7.45(d,J=8.9Hz,1H),7.86(bs,1H),8.03(s,1H),
10.1(bs,1H)MS(SIMS) m/e:. 543$(M+H)^+C_{31}H_{50}N_4O_4$ (542) [0068]Compound ^{1}H-NMR of
Example 13. ($CDCl_3$) delta(ppm):0.88(t,J=6.6Hz,3H),1.16(s,9H),1.20-
1.40(m,22H),2.01(m,2H),4.12(m,2H),4.19(m,1H),4.43-4.54(m,3H),5.45(dd,
J=6.7,15.4Hz,1H),5.72(dt,J=15.4,6.7Hz,1H),5.96(m,1H),6.36(d,J=7.1Hz,1H),7.18-
7.30(m,2H),7.68(m,1H),8.55 (m.) 1HMS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0069]Compound ^{1}H-NMR of Example 14. ($CDCl_3$)
delta(ppm):0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-
1.40(m,22H),2.02(m,2H),4.13(m,2H),4.21(m,1H),4.38(m,2H),4.43(dd,J=7.
7,11.6Hz,1H),5.38(m,1H),5.45(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.7Hz,1H),6.28(d,J=7.4Hz,1
H),7.29(m, 1H, 7.65 (m, 1H), 8.55(m, 2H)MS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0070]Compound ^{1}H-NMR of Example 15. ($CDCl_3$) delta. (ppm) :
0.88(t,J=6.5Hz,3H),1.15(s,9H),1.20-1.44(m,22H),2.02(m,2H),3.72(m,1H),4.13-4.17(m,3H),4.34-
4.48(m,3H), 5.45 () [dd and] J= 6.6-15.4 Hz, 1H, 5.74 (dt, J= 15.3, 6.6 Hz, 1H), 6.29 (d, J= 7.4
Hz, 1H), 7.20 (m, 2H), and 8.57(m, 2H)MS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0071]Compound ^{1}H-NMR of Example 16. ($CDCl_3$) delta. (ppm) :
0.88(t,J=6.6Hz,3H),1.17(s,9H),1.20-
1.40(m,22H),2.01(m,2H),2.97(m,2H),3.61(m,2H),4.06(m,2H),4.16(m,1H), 4.42(dd,J=7.3 11.9
Hz, 1H, 5.43 (dd, J= 6.6-15.3 Hz, 1H), 5.71 (dt, J= 15.4, 6.6 Hz, 1H), 6.39 (d, J= 7.2 Hz, 1H),
7.16 (m, 2H), 7.62 (m, 1H), and 8.53(m, 1H)MS(SIMS) m/e:532$(M+H)^+C_{31}H_{53}N_3O_4$ (531)
[0072]Compound ^{1}H-NMR of Example 17. ($CDCl_3$) delta(ppm) :
0.88(t,J=6.7Hz,3H),1.20(s,9H),1.20-
1.40(m,22H),2.03(m,2H),2.82(m,2H),3.37(m,1H),3.52(m,1H),4.10-4.37(m,
4H),5.40(bs,1H),5.47(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.6,6.3Hz,1H),6.37(d,J=7.0Hz,1H),6.83(s
,1H),7.59(s,1HMS(SIMS) m/e:. 521$(M+H)^+C_{29}H_{52}N_4O_4$ (520) [0073]Compound ^{1}H-NMR
($CDCl_3$) delta (ppm):0.86 (t, Hz [J= 6.4], 3H) of Example 18, 1.07 -
1.42(m,22H),1.15(s,9H),1.87-2.10(m,4H),3.02-3.23(m,3H),4.00(t,J=6.8Hz,2H),4.05-
4.27(m,3H),4.37(dd,J=7. 0,10.9Hz,1H),5.44(dd,J=6.3,15.4Hz,1H),5.62-
5.82(m,2H),6.32(d,J=7.4Hz,1H),6.92(bs,1H),7.03(bs,1H),7.03(bs, 1H, 7.52(bs, 1H)MS(SIMS)

m/e:535$(M+H)^+C_{30}H_{54}N_4O_4$ (534) [0074]Compound ^{1}H-NMR of Example 19. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.81(t,J=6.5Hz,3H),0.96-1.40(m,22H),1.84-2.08(m,2H),4.02-4.50(m,6H),5.45(dd,J=6.4,15.5Hz,1H),5.71(dt, J= 15.5, 6.3 Hz, 1H and 7.08 (d, J= 5.4 Hz, 2H), 7.22-7.53 (m, 2H), 7.71 (d, J= 6.9 Hz, 2H) and 8.28(d, J= 5.4-Hz, 2H)MS(SIMS) m/e:538$(M+H)^+C_{32}H_{47}N_3O_4$ (537) [0075]Compound ^{1}H-NMR of Example 20. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.16(s,9H),1.22-1.40(m,22H),2.02(m,2H),3.56(bs,1H),4.11(m,2H),4.20(m,1H),4.36(m,2H), 4.45(dd,J=7. 6-11.8 Hz, 1H, 5.16 (m, 1H), 5.44 (dd, J= 6.6-15.3 Hz, 1H), 5.72 (dt, J= 15.4, 6.6-Hz, 1H), 6.37 (d, J= 7.0-Hz, 1H), and 7.26-7.40(m, 5H)MS(SIMS) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0076]Compound ^{1}H-NMR of Example 21. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.17(s,9H),1.22-1.40(m,22H),2.02(m,2H),2.94(s,6H),3.69(d,J=5.1Hz,1H),4.08(m,2H),4. 19(m,1H),4.25(m,2H),4.45(dd,J=7.4,11.9Hz,1H),5.00(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.71(dt, J=15.3,6.5Hz, 1H, 6.40 (d, J= 7.0 Hz, 1H), 6.69 (d, J= 8.5 Hz, 2H), 7.14(d, J= 8.5-Hz, 2H)MS(SIMS) m/e:582$(M+Na)^+C_{33}H_{57}N_3O_4$ (559) [0077]Compound ^{1}H-NMR of Example 22. ($CDCl_3$) delta(ppm) : 0.87(t,J=6.4Hz,3H),1.13-1.44(m,22H),1.17(s,9H),1.19-2.11(m,2H),3.15-3.43(m,2H),3.35(bs,1H),3.60-3.82(m, 2H),4.06-4.36(m,4H),5.44(dd,J=6.3,15.4Hz,1H),5.62(t,J=5.7Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.34(d,J=5. 8Hz, 1HMS(CI) m/e :. 471$(M+H)^+C_{26}H_{50}N_2O_5$ (471) [0078]Compound ^{1}H-NMR of Example 23. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.19(s,9H),1.20-1.40(m,22H),1.72(m,2H),2.03(m,2H),2.25(m,1H),3.32(m,1H),3.39(dd,J=5. 0,16.1Hz,1H),3.71(m,2H),4.06-4.16(m,3H),4.39(dd,J=7.6,11.8Hz,1H),5.12(bs,1H),5.45(dd,J=6.6,15.4Hz,1H) and 5.73 (dt and J= 15.3.) 6.8 Hz, 1H, and 6.34(d, J= 7.2-Hz, 1H)MS(SIMS) m/e:485$(M+H)^+C_{27}H_{52}N_2O_5$ (484) [0079]Compound ^{1}H-NMR of Example 24. ($CDCl_3$) delta(ppm):0.86(t,J=6.4Hz,3H),1.06-1.40(m,22H),1.19(s,9H),1.40-1.73(m,4H),1.92-2.08(m,2H),2.32(t,J=7.0Hz,2H),3. 07-3.25(m,2H),3.66(s,3H),3.76(bs,1H),3.96-4.22(m,3H),4.40(m,1H),5.03(t,J=5.7Hz,1H),5.42(dd,J=6.3,15.4Hz, 1H, 5.70 (dt, J= 15.4, 6.5 Hz, 1H) and 6.38(d, J= 6.9-Hz, 1H)MS(SIMS) m/e:541$(M+H)^+C_{30}H_{56}N_2O_6$ (540) [0080]Compound ^{1}H-NMR of Example 25 (500 MHz) $CDCl_3$-CD_3ODdelta. (ppm) : 0.85(t,J=6.3Hz,3H),1.08-1.42(m,22H),1.15(s,9H),1.19-2.12(m,2H),4.16-4.48(m,4H),5.46(dd,J=5.5,15.5Hz, 1H, 5.78 (dt, J= 15.5, 6.5 Hz, 1H) and 6.51(bs, 1H)MS(SIMS) m/e:495$(M+H)^+C_{25}H_{46}N_6O_4$ (494) [0081]Compound ^{1}H-NMR of Example 26. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.46(m,2H),3.35(d,J=5.1Hz,1H),3.47(m,2H),4. 06-4.22(m,3H),4.36(dd,J=7.0,11.7Hz,1H),5.35(bs,1H),5.41-5.54(m,2H),5.68(bs,1H),5.72(dt,J=15.4,6.4Hz, 1H, 6.25(d, J= 7.1-Hz, 1H)MS(SIMS) m/e:498$(M+H)^+C_{27}H_{51}N_3O_5$ (497) [0082]Compound ^{1}H-NMR of Example 27. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),1.75-1.92(m,2H),1.94-2.05(m,2H),2.90-3.03(m,2H),3.22(bs, 2H),3.24-3.36(m,2H),3.65(d,J=4.3Hz,1H),4.00-

4.25(m,3H),4.34(m,1H),5.44(dd,J=5.5,15.1Hz,1H),5.74(dt,J=15.1, 5.9 Hz, 1H, 6.11 (bs, 1H) and 6.37(d, J= 6.4-Hz, 1H)MS(SIMS) m/e:484$(M+H)^+C_{27}H_{53}N_3O_4$ (483) [0083]Compound ^{1}H-NMR of Example 28. ($CDCl_3$) delta(ppm):0.88(t,J=6.4Hz,3H),1.15(d,J=6.9Hz,6H),1.15-1.47(m,22H),1.93-2.11(m,2H),2.37(m,1H),3.21(bs,1H),4.04-4. J= 7.4 Hz of 28(m,3H),4.42(dd,J=6.8,11.1Hz,1H),5.01(bs,2H),5.45(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.06(d, 1HMS(SIMS) m/e:413$(M+H)^+C_{23}H_{44}N_2O_4$ (412) [0084]Compound ^{1}H-NMR of Example 29. ($CDCl_3$) delta(ppm):0.88(t,J=6.4Hz,3H),1.12-1.45(m,22H),1.15(d,J=7.0Hz,6H),1.94-2.12(m,2H),2.38(m,1H),2.74(bs,1H),3.00(d, J=4.5Hz,1H),3.15-3.47(m,2H),3.58-3.85(m,2H),4.08-4.32(m,4H),5.20(bs,1H),5.47(dd,J=6.3,15.4Hz,1H),5.75(dt, J= 15.4, 6.5 Hz, 1H and 6.09(bs, 1H)MS(SIMS) m/e:457$(M+H)^+C_{25}H_{48}N_2O_5$ (456) [0085]Compound ^{1}H-NMR of Example 30. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.18-1.42(m,22H),1.60-1.80(m,2H),1.95-2.10(m,2H),2.37(m,1H),2. 48(bs,1H),3.22-3.42(m,3H),3.70(t,J=5.6Hz,2H),4.04-4.27(m,3H),4.36(dd,J=6.6,10.9Hz,1H),5.21(bs,1H),5.45 (dd, J = 6.3-15.4 Hz) 1H, 5.73 (dt, J= 15.4, 6.6 Hz, 1H), and 6.12(d, J= 7.4-Hz, 1H)MS(SIMS) m/e:471$(M+H)^+C_{26}H_{50}N_2O_5$ (470) [0086]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.9], 3H) of Example 31, 1.14 (d, J= 6.9 Hz, 6H) 1.20-1.47 (m, 22H), 1.59-1.86. (m, 4H), 2.37(m,1H),2.98(m,1H),3.13-3.31(m,2H),3.60-3.75(m,2H),4.00-4.26(m,3H),4.39(dd,J=7.1,9.3Hz,1H),4.95(bs, 1H, 5.46 (dd, J= 6.7-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.5 Hz, 1H), and 6.12(d, J= 6.7-Hz, 1H)MS(SIMS) m/e:485$(M+H)^+C_{27}H_{52}N_2O_5$ (484) [0087]Compound ^{1}H-NMR of Example 32. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.4Hz,3H),1.08-1.50(m,22H),1.97-2.14(m,2H),2.30(s,3H),2.62(m,1H),3.99(m,1H),4.22-4.44(m,2H), 4.98(m,1H),5. 48 (dd, J= 8.3-15.3 Hz, 1H), 5.82 (dt, J= 15.3, 6.6 Hz, 1H), 6.64 (s, 1H), 7.09 (d, J= 8.8 Hz, 2H), and 7.24(d, J= 8.8 Hz, 2H)MS(SIMS) m/e:503$(M+H)^+C_{30}H_{50}N_2O_4$ (502) [0088]Compound ^{1}H-NMR of Example 33 (500 MHz) $CDCl_3$delta. (ppm) : 0.88(t,J=6.8Hz,3H),1.13(d,J=6.4Hz,3H),1.14(d,J=6.6Hz,3H),1.18-1.39(m,22H),1.96-2.08(m,2H),2.37(m,1H), 3.08(bs,1H),3. 80 (s, 3H), 4.11-4.24 (m, 2H), 4.24 (m, 1H), 4.48 (dd, J= 7.3-11.6 Hz, 1H), 5.49 (dd, J= 7.9-15.4 Hz, 1H), 5.70(dt,J=15.4,6.7Hz,1H),6.07(d,J=8.0Hz,1H),6.63(m,1H),6.87(d,J=7.9Hz,1H),6.90(bs,1H),7.09(bs,1H),7.20 (m.) 1HMS(SIMS) m/e:519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0089]Compound ^{1}H-NMR of Example 34. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.14(d,J=6.9Hz,3H),1.21-1.38(m,22H),2.00-2.08(m,2H),2.38(m,1H), 3.25(bs,1H),3. 87 (s, 3H), 4.11-4.25 (m, 2H), 4.28 (m, 1H), 4.50 (dd, J= 7.0, 11.7 Hz, 1H), 5.49 (dd, J= 6.7-15.4 Hz, 1H), 5.75(dt,J=15.4,6.7Hz,1H),6.09(d,J=7.9Hz,1H),6.87(d,J=8.0Hz,1H),6.96(m,1H),7.02(m,1H),7.30(m,1H),8.05(bs,1HMS(SIMS) m/e:. 519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0090]Compound ^{1}H-NMR of Example 35. ($CDCl_3$) delta. (ppm) : 0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1.87-2.05(m,2H),2.32(m,1H), 3.99-4.36(m,4H 5.40 (dd, J= 6.2-15.4 Hz, 1H), 5.68 (dt, J= 15.4, 6.6 Hz, 1H), 6.60 (m, 1H), 6.70 (d, J= 8.7-Hz, 2H), and 7.12(d, J= 8.7-Hz, 2H)MS(CI) m/e:505$(M+H)^+C_{29}H_{47}N_2O_5$ (504)

[0091]Compound ^{1}H-NMR of Example 36. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.4Hz,3H),1.05(d,J=6.9Hz,3H),1.07(d,J=6.8Hz,3H),1.12-1.40(m,22H),1.46(s,9H),1.90-2.07(m,2H), 2.33(m,1H),4. 02-4.38 (m, 4H), 5.41 (dd, J= 6.1-15.4 Hz, 1H), 5.70 (dt, J= 15.4, 6.6 Hz, 1H), 6.56 (d, J= 7.8 Hz, 1H), 6.90 (bs, 1H), and 7.24(s, 4H)MS(SIMS) m/e:504$(M+H)^+C_{29}H_{49}N_3O_4$ (503) [0092]Compound ^{1}H-NMR of Example 37. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.82(t,J=6.4Hz,3H),1.04(d,J=6.6Hz,3H),1.07(d,J=6.6Hz,3H),1.05-1.41(m,22H),1.88-2.08(m,2H),2.33(m,1H), 2.51(s,3H),4. 05-4.40 (m, 4H), 5.42 (dd, J= 6.2-15.4 Hz, 1H), 5.71 (dt, J= 15.4, 6.6 Hz, 1H), 6.58 (d, J= 7.8 Hz, 1H), 7.45 (d, J= 8.8 Hz, 2H) and 7.86(d, J= 8.8-Hz, 2H)MS(SIMS) m/e:531$(M+H)^+C_{31}H_{50}N_2O_5$ (530) [0093]Compound ^{1}H-NMR of Example 38. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.84(t,J=6.2Hz,3H),1.05(d,J=6.9Hz,3H),1.08(d,J=6.9Hz,3H),1.03-1.43(m,22H),1.09-2.09(m,2H),2.34(m,1H), 4.07-4.38(m,4H 5.43 (dd, J= 6.1-15.4 Hz, 1H), 5.73 (dt, J= 15.4, 6.6 Hz, 1H), 6.49 (d, J= 6.3-Hz, 1H) and 7.40-7.65(m, 4H)MS(SIMS) m/e:514$(M+H)^+C_{30}H_{47}N_3O_4$ (513) [0094]Compound ^{1}H-NMR of Example 39. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.45(m,22H),1.88-2.10(m,2H),2.38(m,1H), 2.86(bs,1H),4. 15-4.55 (m, 4H), 5.49 (dt, J= 15.5, 6.3 Hz, 1H), 5.77 (dd, J= 6.5-15.5 Hz, 1H), 6.08 (d, J= 7.7 Hz, 1H), 7.59 (d, J= 9.2 Hz, 2H), 8.12 (bs, 1H), and 8.18(d, J= 9.2-Hz, 2H)MS(SIMS) m/e:534$(M+H)^+C_{29}H_{47}N_3O_6$ (533) [0095]Compound ^{1}H-NMR of Example 40. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.08-1.52(m,22H),1.10(d,J=6.8Hz,3H),1.12(d,J=6.8Hz,3H),1.37(t,J=7.1Hz,3H),1.90-2.11(m,2H),2.38(m,1H),4.14-4.57(m,4H),4.38(q,J=7.1Hz,2H),5.48(dd,J=6.3,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz, 1H, 6.15 (d, J= 7.8 Hz, 1H), 7.46 (d, J= 8.7 Hz, 2H), 7.73 (bs, 1H), 7.98(d, J= 8.7-Hz, 2H)MS(SIMS) m/e:561$(M+H)^+C_{32}H_{52}N_2O_6$ (560) [0096]Compound ^{1}H-NMR of Example 41. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.05(d,J=6.7Hz,6H),1.02-1.47(m,22H),1.90-2.10(m,2H),2.39(m,1H),3.22(bs,1H),3.92(s, 3H),4.13-4.23(m,3H),4.50(m,1H),5.50(dd,J=6.3,15.4Hz,1H),5.74(dt,J=15.4,6,5Hz,1H),6.05(d,J=7.2Hz,1H),7.06 (m, 1H), 7.54 (m, 1H), 8.02 (dd, J= 1.7, 8.0 Hz, 1H), 8.40 (d, J= 8.4 Hz, 1H), 10.60(s, 1H)MS(SIMS) m/e:547$(M+H)^+C_{31}H_{50}N_2O_6$ (546) [0097]Compound ^{1}H-NMR of Example 42. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.48(m,22H),1.90-2.12(m,2H),2.34(m,1H),3.90-4.27(m,3H),4. J= 7.1 Hz of 34(d,J=5.8Hz,2H),4.42(m,1H),5.29(t,J=5.8Hz,1H),5.44(dd,J=6.3,15.5Hz,1H)5.71(dt,J=15.5,6.7 Hz,1H),6.17(d, 1H, 7.16-7.42(m, 5H)MS(CI) m/e503:$(M+H)^+C_{30}H_{50}N_2O_4$ (502) [0098]Compound ^{1}H-NMR of Example 43. ($CDCl_3$) delta(ppm):0.87(t,J=6.2Hz,3H),1.10(d,J=6.8Hz,6H),1.17-1,48(m,22H),1.89-2.11(m,2H),2.34(m,1H),4.08-4.29(m,3H),4. 29-4.48(m,3H),5.45(dd,J=5.9,15.3Hz,1H),5.60(t,J=5.9Hz,1H),5.73(dt,J=15.3,6.7Hz,1H),6.12(d,J=6.9Hz,1H), 7.19 (d, J = 5.3 Hz) 2H and 8.54(d, J= 5.3-Hz, 2H)MS(SIMS) m/e:604$(M+H)^+C_{34}H_{57}N_3O_6$ (603) [0099]Compound ^{1}H-NMR of Example 44. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.17-1.45(m,22H),1.92-

2.10(m,2H),2.32(m,1H), 3.40(bs,1H),4. 02-4.27 (m, 3H), 4.40 (m, 1H), 4.43 (d, J= 6.2 Hz, 2H), 5.31-5.51 (m, 2H), 5.70 (dt, J= 15.4, 6.8 Hz, 1H), 6. 12 (d, J= 7.2-Hz, 1H) and 7.17-7.43(m, 4H)MS(CI) m/e:537 $^{(M+H)^+}C_{30}H_{49}ClN_2O_4$ (536) [0100]Compound ^{1}H-NMR of Example 45. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.45(m,22H),1.92-2.09(m,2H),2.33(s,3H),3.54(bs,1H),4.03-4.
26(m,3H),4.29(d,J=5.7Hz,2H),4.41(dd,J=6.8,11.1Hz,1H),5.24(t,J=5.5Hz,1H),5.44(dd,J=6.2,15.4 Hz,1H),5.71(dt, J= 15.4, 6.3 Hz, 1H, 6.19 (d, J= 7.1 Hz, 1H), and 7.14(s, 4H)MS(SIMS) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0101]Compound ^{1}H-NMR of Example 46. ($CDCl_3$) delta. (ppm) : 0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1,87-2.05(m,2H),2.32(m,1H), 3.99-4.36(m,4H 5.40 (dd, J= 6.2-15.4 Hz, 1H), 5.68 (dt, J= 15.4, 6.6 Hz, 1H), 6.60 (m, 1H), 6.70 (d, J= 8.7 Hz, 2H), and 7.12(d, J= 8.7-Hz, 2H)MS(SIMS) m/e:561$(M+H)^+C_{32}H_{52}N_2O_6$ (560) [0102]Compound ^{1}H-NMR of Example 47. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.48(m,22H),1.91-2.12(m,2H),2.35(m,1H),2.80(t,J=7.0Hz,2H), 3.31-3.56(m,3H 3.99-4.26 (m, 3H), 4.38 (dd, J= 6.7-11.2 Hz, 1H), 4.92 (t, J= 5.3 Hz, 1H), 5.44 (dd, J= 6.3-15.4 Hz, 1H), 5.71 (dt, J= 15.4, 6.5 Hz, 1H), 6.13 (d, J= 7.3-Hz, 1H) and 7.10-7.38(m, 5H)MS(CI) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0103]Compound ^{1}H-NMR of Example 48. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.12-1.45(m,22H),1.93-2.11(m,2H),2.20-2.56(m,8H),3.18-3.38(m,2H), 3.64-3.79(m, 4H, 4.01-4.28 (m, 3H), 4.40 (dd, J= 6.4-15.4 Hz, 1H), 5.73 (dt, J= 15.4, 6.5-Hz, 1H) and 6.12(d, J= 7.1-Hz, 1H)MS(CI) m/e526$(M+H)^+C_{29}H_{55}N_3O_5$ (525) [0104]Compound ^{1}H-NMR of Example 49. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.6Hz,3H),1.05(d,J=6.7Hz,3H),1.07(d,J=6.7Hz,3H),1.05-1.45(m,22H),1.85-2.08(m,2H),2.33(m,1H), 4.05-4.50(m,4H 5.42 (dd, J= 6.3-15.5 Hz, 1H), 5.73 (dt, J= 15.5, 6.7 Hz, 1H), 6.57 (d, J= 8.0-Hz, 1H), 6.87 (d, J= 3.5-Hz, 1H), and 7.31(d, J= 3.5-Hz, 1H)MS(CI) m/e:496$(M+H)^+C_{26}H_{45}N_3O_4S$ (495) [0105]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.87 (t, Hz [J= 6.4], 3H) of Example 50, 1.00-1.45 (m, 22H), 1.11 (d, J= 6.8 Hz, 6H), 1.90-2.10. (m, 2H), and 2.35(m,1H),3.05(bs,1H),4.14-4.38(m,3H),4.50(m,1H),5.50(dd,J=6.2,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz,1H),6.15 (d.) J= 7.7 Hz, 1H, 7.40 (m, 1H), 7.65 (m, 1H), 7.76 (d, J= 7.9-Hz, 1H), 7.83 (d, J= 8.4-Hz, 1H), and 8.15(s, 2H)MS(CI) m/e:540$(M+H)^+C_{32}H_{49}N_3O_4$ (539) [0106]Compound ^{1}H-NMR of Example 51. ($CDCl_3$) delta. (ppm) : 0.88(t,J=7.0Hz,3H),1.07(d,J=6.9Hz,2H),1.09(d,J=6.9Hz,2H),1.18-1.40(m,22H),1.97-2.09(m,2H),2.32(m,1H), 4.13-4.25(m,2H 4.34 (dd, J= 3.2-11.6 Hz, 1H), 4.41 (dd, J= 7.6-11.6 Hz, 1H), 4.66 (d, J= 15.9 Hz, 1H), 4.75 (d, J= 15.9 Hz) J= 4.7 Hz of 1H),5.48 (dd,J=6.3,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.19(d,J=7.6Hz,1H),7.26(d,J=4.7Hz,2H),8.43(d, 2HMS(SIMS) m/e:520 $^{(M+H)^+}C_{29}H_{49}N_3O_5$ (519) [0107]Compound ^{1}H-NMR of Example 52. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.20-1.36(m,20H),1.60(m,2H),1.71(d,J=6.4Hz,1H),2.17(m,2H),4.10-4.19(m,2H),4.21(m, 1H),4.27(m,1H),4.35(d,J=2.9Hz,1H),5.49(m,1H),5.76(m,1H),6.28(bd,1H),6.38(bd,1H),7.23(d,J= 5.6Hz,1H),8.53 (d, J= 5.3 Hz, 1H) [0108]Compound ^{1}H-NMR of Example 53. ($CDCl_3$) delta. (ppm) :0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.05-1.50(m,22H),1.90-

2.16(m,2H),2.34(m,1H),3.98-4.52(m,6H),5. 34-5.60 (m.) 2H, 5.73 (dt, J= 15.4, 6.8 Hz, 1H), 6.10 (d, J= 7.1 Hz, 1H), 7.19 (d, J= 5.5-Hz, 1H) and 8.55(d, J= 5.5-Hz, 1H)MS(CI) m/e406$(M+H)^+C_{22}H_{35}N_3O_4$ (405) [0109]Compound ^{1}H-NMR of Example 54 (500 MHz) $CDCl_3$delta(ppm): 0.88(t,J=6.9Hz,6H),1.18-1.40(m,34H),1.53-1.69(m,4H),1.96-2.10(m,2H),2.11-2.22(m,2H),3.07(bs,1H),4.11-4. 20(m,2H),4.25(m,1H),4.34-4.44(m,3H),5.31(t,J=6.1Hz,1H),5.47(dd,J=6.6,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz, 1H, 6.01 (d, J= 8.0 Hz, 1H), 7.20 (d, J= 5.8 Hz, 2H), 8.57(d, J= 5.8-Hz, 2H)MS(SIMS) m/e:602$(M+H)^+C_{36}H_{63}N_3O_4$ (601) [0110]Compound ^{1}H-NMR of Example 55. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.10(d,J=6.8Hz,6H),1.12-1.47(m,16H),1.90-2.13(m,2H),2.33(m,1H),3.40(bs,1H),4.04-4. 50(m,6H),5.44(dd,J=6.2,15.5Hz,1H),5.57-5.82(m,2H),6.14(d,J=7.3Hz,1H),7.23(d,J=5.8Hz,2H),8.53(d,J=5.8Hz,2HMS(SIMS) m/e:. 462$(M+H)^+C_{26}H_{43}N_3O_4$ (461) [0111]Compound ^{1}H-NMR of Example 56. ($CDCl_3$) delta(ppm):0.87(t,J=6.3Hz,3H),1.10(d,J=6.7Hz,6H),1.10-1.46(m,16H),1.90-2.10(m,2H),2.33(m,1H),3.35(bs,1H),3.90(s, J= 8.1 Hz of 3H),4.04-4.27(m,3H),4.31-4.51(m,3H),5.33-5.65(m,2H),5.72(dt,J=15.2,6.5Hz,1H),6.14(d,J=7.2Hz,1H),7.33(d, 2H, 7.99(d, J= 8.1-Hz, 2H)MS(SIMS) m/e:519$(M+H)^+C_{29}H_{46}N_2O_6$ (518) [0112]Compound ^{1}H-NMR of Example 57. ($CDCl_3$) delta(ppm):0.88(t,J=6.3Hz,3H),1.15(d,J=6.9Hz,6H),1.11-1.46(m,16H),1.94-2.13(m,2H),2.37(m,1H),3.17(bs,1H),4.06-4. J= 7.1 Hz of 29(m,3H),4.39(dd,J=6.8,11.1Hz,1H),4.74(bs,2H),5.45(dd,J=6.5,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz,1H),6.06(d, 1HMS(CI) m/e:371$(M+H)^+C_{20}H_{38}N_2O_4$ (370) [0113]Compound ^{1}H-NMR of Example 58. ($CDCl_3$) delta(ppm):0.86(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.13-1.43(m,16H),1.90-2.08(m,2H),2.21(s,6H),2.36(m,1H),2.40(t, J=6.3Hz,2H),2.47(bs,1H),3.24(m,2H),4.00-4.23(m,3H),4.39(dd,J=6.0,11.1Hz,1H),5.44(dd,J=6.4,15.4Hz,1H), 5.58 (m, 1H), 5.71 (dt, J= 15.4, 6.4-Hz, 1H) and 6.29(d, J= 7.2-Hz, 1H)MS(CI) m/e:442$(M+H)^+C_{24}H_{47}N_3O_4$ (441) [0114]Compound ^{1}H-NMR of Example 59. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.19(s,9H),1.20-1.40(m,26H),2.03(m,2H),3.32(d,J=5.4Hz,1H),4.10(dd,J=3.8,11.9Hz,1H), 4.14(m,1H),4. 21 (m, 1H), 4.41 (dd, J= 7.6-11.8 Hz, 1H), 4.69 (bs, 2H), 5.45 (dd, J= 6.7-15.4 Hz, 1H), 5.74 (dt, J= 15.3, 6.8 Hz, 1H) and 6.29(d, J= 7.4-Hz, 1H)MS(SIMS) m/e:455$(M+H)^+C_{26}H_{50}N_2O_4$ (454) [0115]Compound ^{1}H-NMR of Example 60. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.15(s,9H),1.20-1.40(m,26H),2.02(m,2H),3.33(bs,1H),4.13(m,2H),4.20(m,1H),4.32-4.49(m, J= 7.7 Hz of 3H),5.25(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.28(d,J=7.4Hz,1H),7.28(m,1H),7.63(d, 1H, 8.55(m, 2H)MS(SIMS) m/e:546$(M+H)^+C_{32}H_{55}N_3O_4$ (545) [0116]Compound ^{1}H-NMR of Example 61. ($CDCl_3$) delta(ppm):0.88(t,J=6.6Hz,6H),1.08-1.43(m,52H),1.93-2.10(m,2H),2.17(t,J=7.5Hz,2H),2.98(bs,1H),4.10-4.44(m,6H),5. 34(t,J=6.3Hz,1H),5.47(dd,J=6.6,15.6Hz,1H),5.74(dt,J=15.6,6.6Hz,1H),6.00(d,J=6.9Hz,1H),7.20(d,J=5.5Hz, 2H, 8.57(d, J= 5.5-Hz, 2H)MS(SIMS) m/e:700$(M+H)^+C_{43}H_{77}N_3O_4$ (699) [0117]Compound ^{1}H-NMR of Example 62. ($CDCl_3$) delta. (ppm) :0.87(t,J=6.4Hz,3H),1.08-

1.45(m,22H),1.93-2.11(m,2H),2.00(s,3H),3.14(bs,1H),4.03-4.28(m,3H),4.34(dd,J=6.2-10.6Hz, 1H, 4.86 (bs, 2H), 5.47 (dd, J= 6.2-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.5 Hz, 1H) and 6.13(d, J= 6.8-Hz, 1H)MS(SIMS) m/e:385$(M+H)^+C_{21}H_{40}N_2O_4$ (384) [0118]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.6], 3H) of Example 63, 1.18 (s, 9H), 1.20-1.44 (m, 22H), 1.90-2.12 (m, 4H), 2.88 (d, J= 4.9 Hz, 3H), 2.90 (s, 6H), 2.96-3.54 (m, 4H), 4.12-4.40 (m, 3H), 5.48 (m, 1H) and 5.78 (dt, J= 15.2, 6.6 Hz, 1H), 6.33(m, 1H)MS(SIMS) m/e:526$(M+H)^+C_{30}H_{59}N_3O_4$ (525) [0119]Compound ^{1}H-NMR of Example 64. ($CDCl_3$) delta. (ppm) : 0.79(t,J=6.3Hz,3H),1.00(d,J=6.8Hz,3H),1.03(d,J=6.8Hz,3H),1.00-1.40(m,22H),1.84-2.05(m,2H),2.04(s,3H), 2.30(m,1H),3. 98-4.35 (m, 4H), 5.38 (dd, J= 6.3-15.4 Hz, 1H), 5.66 (dt, J= 15.4, 6.6 Hz, 1H), 6.72 (d, J= 7.9 Hz, 1H), 7.23 (d, J= 8.9 Hz, 2H) and 7.35(d, J= 8.9-Hz, 2H)MS(SIMS) m/e:546$(M+H)^+C_{31}H_{51}N_3O_5$ (545) [0120]Example 653-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (30 mg, 0.062mmol) is melted in a tetrahydrofuran (0.5 ml), Triethylamine (one drop) and methyliso cyanate (90 mg, 0.92mmol) were added, and it stirred at 60 ** for 6 hours. The reaction mixture was melted after concentration, the residue was melted in the tetrahydrofuran (0.5 ml) by decompression, tetrabutylammonium fluoride (tetrahydrofuran 1M solution, 0.80 ml) was added, and it stirred at the room temperature for 4 hours. Column chromatography refined the residue and 1-O-methylamino carbonyl 2-N-isobutyryl D-erythro sphingosine (16 mg) was obtained. ^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.45(m,22H),1.90-2.10(m,2H),2.36(m,1H),2.77(d,J=4.9Hz,3H), 3.58(bs,1H),3. 98-4.25 (m, 3H), 4.38 (dd, J= 6.8-11.2 Hz, 1H), 4.96 (m, 1H), 5.44 (dd, J= 6.3-15.4 Hz, 1H), 5.71 (dt, J= 6.4-15.4 Hz, 1H) and 6.21(d, J= 7.1-Hz, 1H)MS(CI) m/e:427$(M+H)^+C_{24}H_{46}N_2O_4$ (426) [0121]The compound of Examples 65-71 was manufactured like the method of 66 to example 72 Example 65. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown.

Compound ^{1}H-NMR of Example 66. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,3H),1.13(d,J=6.8Hz,3H),1.13-1.46(m,22H),1.92-2.11(m,2H),2.37(m,1H), 3.17(bs,1H),4. 10-4.37 (m, 3H), 4.47 (dd, J= 6.8-10.8 Hz, 1H), 5.48 (dd, J= 6.3-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.9 Hz, 1H), 6.14 (d, J= 7.6 Hz, 1H), 7.07 (m, 1H), 7.13 (bs, 1H), and 7.23-7.44(m, 4H)MS(CI) m/e489$(M+H)^+C_{29}H_{48}N_2O_4$ (488) [0122]Compound ^{1}H-NMR of Example 67. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.11(d,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.42(m,22H),1.91-2.10(m,2H),2.38(m,1H), 3.00(m,1H),4. 16-4.57 (m, 4H), 5.48 (dd, J= 6.3-15.4 Hz, 1H), 5.78 (dt, J= 15.4, 6.5 Hz, 1H), 6.09 (d, J= 7.8 Hz, 1H), 7.25-7. 49 (m, 2H), 7.49-7.65 (m, 2H), and 7.72(bs, 1H)MS(CI) m/e557$(M+H)^+C_{30}H_{47}F_3N_2O_4$ (556) [0123]Compound ^{1}H-NMR of Example 68. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.8Hz,3H),1.04-1.46(m,22H),1.92-2.12(m,2H),2.37(m,1H), 3.21(bs,1H),3. 78 (s, 3H), 4.10-4.35 (m, 3H), 4.46 (dd, J= 6.7-10.9 Hz, 1H), 5.47 (dd, J= 6.3-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.6 Hz, 1H), 6.11 (d, J= 7.4-Hz, 1H), 6.74-6.94 (m, 2H), and 7.14-7.38(m, 2H)MS(CI) m/e:519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0124]Compound ^{1}H-NMR of Example 69. ($CDCl_3$) delta. (ppm) :

0.88(t,J=6.4Hz,3H),1.12(d,J=6.8Hz,3H),1.14(d,J=6.8Hz,3H),1.10-1.45(m,22H),1.92-2.12(m,2H),2.38(m,1H), 3.00(bs,1H),3. 87 (s, 3H), 4.14-4.38 (m, 3H), 4.49 (m, 1H), 5.49 (dd, J= 6.3-15.4 Hz, 1H), 5.76 (dt, J= 15.4, 6.6 Hz, 1H), 6.07 (d, J= 7.8 Hz, 1H), 7.22 (bs, 1H), 7.38 (m, 1H), 7.62-7.81 (m, 2H), and 7.98(s, 1H)MS(SIMS) m/e:547$(M+H)^+C_{31}H_{50}N_2O_6$ (546) [0125]Compound ^{1}H-NMR of Example 70. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.06(t,J=6.8Hz,3H),1.09(t,J=6.8Hz,3H),1.11-1.48(m,22H),1.90-2.12(m,2H),2.32(m,1H), 4.08-4.43(m,4H 5.42 (dd, J= 5.9-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.7 Hz, 1H), 6.14 (d, J= 7.7-Hz, 1H), 7.47-7.71 (m, 3H), and 7.95-8.09(m, 2H)MS(SIMS) m/e:575$(M+Na)^+C_{29}H_{48}N_2O_6S$ (552) [0126]Compound ^{1}H-NMR of Example 71. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.21(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.55(d,J=7.0Hz,1H),4.24(m,2H),4.49(m,2H),5. 53(dd,J=5.9,15.5Hz,1H),5.82(dt,J=15.6,6.7Hz,1H),6.58(d,J=7.4Hz,1H),7.51(m,2H),7.62(m,1H), 7.85(m,1H),8.31 (s, 1H) [0127]Compound ^{1}H-NMR of Example 72. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.29(t,J=7.1Hz,3H),2.02(m,2H),3.20(bs,1H),3.39(d,J=5. 1Hz,2H),4.05-4.25(m,3H),4.23(q,J=7.2Hz,2H),4.45(dd,J=6.2,11.1Hz,1H),5.31(m,1H),5.45(dd,J=6.6,15.4Hz, 1H, 5.74(dt,J=15.4,6.5Hz,1H),6.26(d,J=6.7Hz,1H) [0128]In the tetrahydrofuran (1 ml) solution of example 734-(methylthio) aniline (56 mg, 0.4mmol). After adding 2 di-tert-butyl carbonate (109 mg, 0.50mmol) and adding N,N-dimethylamino pyridine (49 mg, 0.4mmol) subsequently, it stirred for 30 minutes at the room temperature. The tetrahydrofuran (1 ml) solution of 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (48 mg, 0.10mmol) was added to this reaction mixture, and it stirred at the room temperature for 12 hours. It condensed under decompression of this reaction mixture, column chromatography refined the residue, and 1-O-[4-(methylthio) anilinocarbonyl]-2-N-isobutyryl 3-O-(tert-butyldimethylsilyl)-D-erythro sphingosine (30 mg) was obtained.
^{1}H-NMR ($CDCl_3$) delta (ppm):0.00 (s, 3H), 0.03. (s, 3H), 0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.11(d,J=6.9Hz,3H),1.12-1.55(m,22H),1.92-2.12(m,2H), 2.31(m,1H),2. 45 (s, 3H), 4.10-4.30 (m, 3H), 4.48 (m, 1H), 5.41 (dd, J= 6.2-15.5 Hz, 1H), 5.67 (dt, J= 15.5, 6.7 Hz, 1H), 5.85 (d, J= 8.1 Hz, 1H), 6.95 (s, 1H), and 7.15-7.40 (m, 4H) [0129]The compound (30 mg, 0.046mmol) obtained here was melted in the tetrahydrofuran (1 ml), the bottom tetrabutylammonium fluoride of ice-cooling (0.5 ml as 1M solution) was added, and it stirred under the temperature for 5 hours. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. With magnesium sulfate, after desiccation, it condensed, column chromatography refined the residue, and 1-O-[4-(methylthio) anilinocarbonyl]-2-N-isobutyryl D-erythro sphingosine (14 mg) was obtained.
^{1}H-NMR. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.81(t,J=6.3Hz,3H),1.02(d,J=6.7Hz,3H),1.05(d,J=6.9Hz,3H),0.90-1.40(m,22H),1.84-2.05(m,2H),2.32(m,1H), 3.20(s,3H),3. 95-4.38 (m, 4H), 5.39 (dd, J= 6.2-15.3 Hz, 1H), 5.68 (dt, J= 15.3, 6.6 Hz, 1H), 6.65 (d, J= 7.9 Hz, 1H), 7.15 (d, J= 8.6 Hz, 2H) and 7.27(d, J= 8.6-Hz, 2H)MS(SIMS) m/e:535$(M+H)^+C_{30}H_{50}N_2O_4S$ (534) [0130]Example 753-O-(tert-

butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (0.90 mg, 1.8mmol) is melted in the mixed solvent of dimethyl sulfoxide (12 ml) and a tetrahydrofuran (12 ml), It ice-cooled, after adding triethylamine (6 ml). The sulfur trioxide pyridine complex (2.84 g, 18mmol) was added to this solution, and it stirred for 30 minutes. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. The extract was condensed after desiccation with magnesium sulfate, column chromatography refined the residue, and (1'S,2'R,3'E)-N-[2-(tert-butyldimethylsilyloxy)-1-formyl-3-heptadecenyl] PIBARU amide (aldehyde object) (0.80g) was obtained.

^{1}H-NMR. ($CDCl_3$) delta. (ppm) :0.00(s,3H),0.01(s,3H),0.86(s,9H),0.89(t,3H),1.23(s,9H),1.23-1.38(m,22H),2.08(m,2H),4.48-4.57(m,2H),5.67 (dd and J= 6.0.)
15.4Hz,1H),5.89(dt,J=15.2,7.0Hz,1H),6.52(d,J=6.1Hz,1H),9.71(s,1H) [0131]The aldehyde object (0.86 g,1.8mmol) and hydroxylamine hydrochloride (0.47 g,6.7mmol) which were obtained here were melted in the tetrahydrofuran (12 ml), N,N-diisopropylethylamine (1.16 g, 9.0mmol) was added, and it stirred at the room temperature for 3 hours. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[-(tert-butyldimethylsilyloxy)-1-hydroxy imino methyl-3-heptadecenyl] PIBARU amide (hydroxylimine object) (0.88g) was obtained.

[0132]The hydroxylimine object (3.18 g, 6.2mmol) acquired here was melted in the tetrahydrofuran (50 ml), and under ice-cooling, an acetic anhydride (0.70 ml) and pyridine (0.70 ml, 8.7mmol) were added one by one, and were stirred for 20 minutes. Water was added to reaction mixture and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[1-acetoxy imino methyl-2-(tert-butyldimethylsilyloxy)-3-heptadecenyl] PIBARU amide (acetoxyimine object) (2.53g) was obtained.

^{1}H-NMR. ($CDCl_3$) delta(ppm):0.01(s,3H),0.04(s,3H),0.88(s,9H),0.88(t,3H),1.21(s,9H),1.21-1.40(m,22H),2.03(m,2H),2.16(s,3H),4.40(m,
1H),4.66(m,1H),5.43(dd,J=6.7,15.5Hz,1H),5.74(dt,J=15.4,6.8Hz,1H),6.34(d,J=7.3Hz,1H),7.75(d,J=4.6Hz,1H) [0133]In the ethanol (200 ml) solution of the acetoxyimine object (2.53 g, 4.6mmol) acquired here. After adding molybdic acid (5.48 g,37.5mmol), sodium borohydride (4.79 g, 127mmol) was added under -30 ** cooling, temperature up was carried out to 0 **, and it stirred at the temperature for 48 hours. The ammonia solution was added to reaction mixture 10%, and ethyl acetate extracted. With magnesium sulfate, after desiccation, it condensed, column chromatography refined the residue, and (1'S,2'R,3'E)-N-[1-aminomethyl 2-(tert-butyldimethylsilyloxy)-3-heptadecenyl] PIBARU amide (amine object) (1.32g) was obtained.

[0134]In next, the dichloromethane (5 ml) solution of 4-dimethylaminopyridine (73 mg, 0.6mmol). After adding 2 di-tert-butyl carbonate (0.15 mg, 0.7mmol) and adding 4-pyridylmethylamine (65 mg, 0.6mmol) subsequently, it stirred for 30 minutes at the room temperature. The amine object (99 mg, 0.2mmol) acquired by this reaction mixture at the previous reaction was added, and it stirred at the room temperature for 5 hours. Column

chromatography refines a residue after condensing reaction mixture, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - (tert-butyldimethylsilyloxy)-1-[-- [-- three - (4-pyridyl methyl) -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (ureido object) (94 mg) -- having obtained . [0135]The ureido object (93 mg, 0.15mmol) acquired here was melted in the tetrahydrofuran (1.8 ml), the bottom tetrabutylammonium fluoride of ice-cooling (1.8 ml as 1M solution) was added, and it stirred for 20 minutes under the temperature. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. magnesium sulfate -- desiccation -- after -- condensing -- a residue -- column chromatography -- refining -- (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - hydroxy- -- one - [-- [-- three - (4-pyridyl methyl) -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (94 mg) -- having obtained . ^{1}H-NMR. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.12(s,9H),1.20-1.40(m,22H),2.02(m,2H),3.27(dt,J=4.9,14.4Hz,1H),3.50(m,1H),3.87(m, 1H),4.10(m,1H),4.35(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.58(bs,1H),5.64(bs,1H),5.73(dt,J=15.4, 6.6Hz,1H),6.65 (d, J= 6.4 Hz, 1H), 7.19 (d, J= 4.6 Hz) and 8.51(bs, 1H)MS(SIMS) m/e:517$(M+H)^+C_{30}H_{52}N_4O_3$ (516) [0136]The compound of Examples 76-78 was manufactured like the method of 76 to example 78 Example 75. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown. Compound ^{1}H-NMR of Example 76. ($CDCl_3$) delta. (ppm) :0.88(t,J=7.1Hz,3H),1.19(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.25(m,1H),3.50(m,1H),3.72(bs,1H),3.91(m,1H), and 4.11 (m.) 1H, 4.59 (bs, 2H), 5.28 (bs, 1H), 5.47 (dd, J= 6.6-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.8 Hz, 1H) and 6.61(bs, 1H)MS(SIMS) m/e:426$(M+H)^+C_{24}H_{47}N_3O_3$ (425) [0137]Compound ^{1}H-NMR of Example 77. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.76(d,J=4.9Hz,1H),3.25(dt,J=14.4,4.9Hz,1H), 3.54(m,1H),3. 90 (m, 1H), 4.02 (m, 1H), 4.09 (m, 1H), 4.59 (bs, 1H), 4.96 (t, J= 5.9 Hz, 1H), 5.47 (dd, J= 6.5-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.6 Hz, 1H), and 6.71(d, J= 6.5-Hz, 1H)MS(SIMS) m/e:462$(M+Na)^+C_{25}H_{49}N_3O_3$ (439) [0138]Compound ^{1}H-NMR of Example 78. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.37(J=7.1Hz,3H),2.01(m,2H),3.36(dt,J=14.5,4.9Hz,1H), 3.56(m,1H),3.94(m,1H),4.17(m,1H),4.34(m,2H),5.50(dd,J=6.4,15.5Hz,1H),5.77(dt,J=15.0,6.7Hz ,1H),6.01(bs, 1H, 6.58 (d, J= 7.2 Hz, 1H), 7.45 (d, J= 8.5 Hz, 1H), 7.68 (bs, 1H), 7.95(d, J= 8.7-Hz, 1H)MS(SIMS) m/e:596$(M+Na)^+C_{33}H_{55}N_3O_5$ (573) [0139]Example 79. (1'S, 2'R, 3'E)-N-[-1-aminomethyl 2-. (tert-butyldimethylsilyloxy) Pyridine (31 mg, 0.4mmol) is added to the tetrahydrofuran (4 ml) solution of]-3-heptadecenyl] PIBARU amide (amine object) (99 mg, 0.2mmol), -It warmed to -20 ** over 1 hour after dropping bottom chloro CHIONOGI acid phenyl of 78 ** cooling (41microl, 0.3mmol). Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[2-(tert-butyldimethylsilyloxy)-1-(phenoxythiocarbonyl aminomethyl)-3-heptadecenyl] PIBARU amide (42 mg) was obtained. ^{1}H-NMR. ($CDCl_3$) delta(ppm):0.09(s,3H),0.88(t,J=7.1Hz,3H),0.94(s,9H),1.22(s,9H),1.20-1.43(m,22H),2.06(m,2H),3.78-3.92(m,2H),4.10(m,

1H),4.34(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz,1H),6.32(d,J=7.7Hz,1H),7.04(d,J=7.9Hz,1H), 7.25 (d, J = 7.9 Hz) 1H),7.38(d,J=7.9Hz,1H),7.89(m,1H) [0140]After melting the compound (86 mg, 0.14mmol) obtained here in dimethyl sulfoxide (1 ml), 4-pyridylmethylamine (15microl) was added and it stirred at the room temperature for 5 hours. Water was added to reaction mixture and ethyl acetate extracted. After drying with magnesium sulfate after rinsing and distilling off a solvent, column chromatography refines a residue, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - (tert-butyldimethylsilyloxy)-1-[-- [-- three - (4-pyridyl methyl) -- thio -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (thio ureido object) (61 mg) -- having obtained .

[0141]The thio ureido object (60 mg, 0.10mmol) acquired here was melted in the tetrahydrofuran (1.1 ml), the bottom tetrabutylammonium fluoride of ice-cooling (tetrahydrofuran 1M solution, 1.1 ml) was added, and it stirred under ice-cooling for 6 hours. Water was added to reaction mixture and ethyl acetate extracted. After drying with magnesium sulfate after rinsing and distilling off a solvent, column chromatography refines a residue, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - hydroxy- -- one - [-- [-- three - (4-pyridyl methyl) -- thio -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (35 mg) -- having obtained .

^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-1.43(m,22H),2.07(m,2H),3.65(m,1H),3.90(bs,1H),4.23(m,1H),4.76(bs, 2H, 5.50 (dd, J= 6.4-15.3 Hz, 1H), 5.81 (dt, J= 15.2, 6.9 Hz, 1H), 6.44 (bs, 1H), 7.26 (m, 2H), and 8.54(d, J= 5.6-Hz, 2H)MS(SIMS) m/e:533$(M+H)^+$$C_{30}H_{52}N_4O_2S$ (532) [0142]Example 803-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (40 mg, 0.08mmol) is melted in dichloromethane (1 ml), -The bottom pyridine of 78 ** cooling (66 mg, 0.83mmol) was added, subsequently chloroformic acid trichloromethyl (26 mg, 0.13mmol) was added, and temperature up was carried out to -20 ** over 1 hour. 4-(tert-butoxycarbonylamino) aniline (87 mg, 0.42mmol) was dropped at this reaction mixture, and temperature up was carried out to the room temperature over 1 hour. After stirring reaction mixture at a room temperature for 13 hours, chloroform extracted it. The extract was rinsed after saturated sodium bicarbonate water subsequently washed, 1M chloride and. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, 1-O--3-[[[4-(tert-butoxycarbonylamino) phenyl] aminocarbonyl]] O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (25 mg) was obtained.

^{1}H-NMR. ($CDCl_3$)
delta(ppm):0.00(s,3H),0.30(s,3H),0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.15-1.42(m, 22H),1.50(s,9H),1.92-2.09(m,2H),2.30(m,1H),4.05-4.28(m,3H),4.48(m,1H),5.42(dd,J=6.2,15.4Hz,1H),5.67(dt, J= 15.4, 6.7 Hz, 1H),5.86(d,J=7.8Hz,1H),6.46(s,1H),6.81(s,1H),7.20-7.33(m,4H) [0143]The compound (13 mg, 0.02mmol) obtained here was melted in ethyl acetate (0.7 ml), the bottom of ice-cooling 4M hydrogen chloride-ethyl acetate solution (0.3 ml) was added, and it stirred for 30 minutes under the temperature. Reaction mixture was condensed by decompression, refined the residue with thin layer chromatography, and obtained 1-O-[(4-aminophenyl) aminocarbonyl]-2-N-isobutyryl

D-erythro sphingosine (8 mg).
^{1}H-NMR. ($CDCl_3$-CD_3CD) delta. (ppm) :
0.79(t,J=6.4Hz,3H),1.01(d,J=6.8Hz,3H),1.02(d,J=6.9Hz,3H),1.00-1.40(m,22H),1.82-2.10(m,2H),2.30(m,1H), 3.92-4.30(m,4H 5.37 (dd, J= 6.3-15.4 Hz, 1H), 5.65 (dt, J= 15.4, 6.2 Hz, 1H), 6.58 (d, J= 8.4 Hz, 2H), 6.74 (bs, 1H), 7.07 (d, J= 8.4 Hz, 2H), and 8.20(s, 1H)MS(SIMS) m/e:504$(M+H)^+$$C_{29}H_{49}N_3O_4$ (503) [0144]In the chloroform (1 ml) solution of example 811-O-[[3-(dimethylamino) propyl] Aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine (40 mg). Potassium bicarbonate (0.5g) was added, subsequently the methyl iodide (0.5 ml) was added, and it stirred at the room temperature for 16 hours. It condenses, after filtering a sludge, and it is 1-O-[[3-(trimethylammonio) propyl] Aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine. Iodine salt (28 mg) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.20(s,9H),1.20-1.44(m,22H),2.02(m,2H),2.13(m,2H),3.38(s,9H),3.38(m,1H),3.56(bs,1H), 3.84(m,2H),4 . 17 (m, 2H), 4.26 (m, 1H), 4.31 (dd, J= 5.6-11.1 Hz, 1H), 5.48 (dd, J= 6.8-15.4 Hz, 1H), 5.80 (dt, J= 15.2, 6.8 Hz, 1H), 6.25 (m, 1H) and 6.36(d, J= 8.5-Hz, 1H)MS(SIMS) m/e:526(M-127)$^+$$C_{30}H_{60}IN_3O_4$ (654) [0145]Example 823-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (0.20 g, 0.4mmol) was melted in dichloromethane (8 ml), and it cooled at -78 **. Pyridine (320microl, 4.0mmol) was added to this solution, subsequently chloroformic acid trichloromethyl (58microl-0.48mmol) was added to it, and temperature up was carried out to it to -20 ** over 1 hour. After adding the dichloromethane (5 ml) solution of 2-aminoethanol (340microl, 4.0mmol), temperature up was carried out to the room temperature over 4 hours. 1M chloride, saturated sodium bicarbonate water, water, and a saturation salt solution washed reaction mixture one by one. Distill off a solvent after desiccation with magnesium sulfate, and column chromatography refines a residue, 3-O-(tert-butyldimethylsilyl)-1-O-[(2-hydroxyethyl) aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine (0.22g) was obtained.